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CONTENTS

	PAGE
The Infant with Stridor. JOHN APLEY	423
The Results of a National Inquiry into the Growth of Premature Children from Birth to 4 Years. J. W. B. DOUGLAS and C. MOGFORD	436
The Excretion of Sugars after the Intravenous Administration of Invert Sugar. J. H. P. JONXIS and T. H. J. HUISMAN	446
Some Observations on Umbilical Hernia in Infants. GRACE E. WOODS	450
Involution of the Left Liver in the Newborn and its Relationship to Physiological Jaundice. JOHN L. EMERY	463
The Pattern of Haemolytic Disease of the Newborn. BARBARA S. DAVIES, JOHN GERRARD and J. A. H. WATERHOUSE	466
Duodenal Ulcers with Extensive Liver Damage in Infant Twins. J. L. KNIPTON and MARTIN BODIAN	471
Poisoning by the Volatile Oils in Childhood. J. O. CRAIG	475
Boric Acid Poisoning in Infancy Arising from the Treatment of Napkin Rash. P. C. MACGILLIVRAY AND M. S. FRASER	484
Haemangio-endothelioma with Haemorrhage and Thrombocytopenia. A. WILLIS FRANKLIN and D. A. J. WILLIAMSON	490
A History of Infant Feeding. Part V.—Nineteenth Century Concluded and Twentieth Century. IAN G. WICKES	495
Index to Volume 28	503

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THE INFANT WITH STRIDOR

A FOLLOW-UP SURVEY OF 80 CASES

BY

JOHN APLEY

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(RECEIVED FOR PUBLICATION JUNE 19, 1953)

It is a tendency of specialists in any field to examine all phenomena exclusively with the instruments of their own speciality. Infantile stridor has been a perquisite of laryngologists for so long that it is not surprising to find the many descriptions of it devoted largely to laryngeal factors. A great deal of attention has been paid to the larynx but very little to the infant. As a result, information regarding associated conditions, complications and sequelae, prognosis and mortality has been neglected. This paper records follow-up observations on 80 infants who had stridor. The sole criterion for inclusion was the occurrence of sustained stridor in early infancy. The data include observations on stridor itself, on the infants who presented with it, and on the mechanism and aetiology of its production.

Stridor

The Oxford English Dictionary defines stridor as: 'A harsh vibratory sound produced by a bronchial, tracheal or laryngeal obstruction'. Wilson (1952a) rightly affirms that stridor 'may be caused by almost any lesion of the respiratory system'. The primary abnormality may, however, occur in the neck or thorax or in the nervous system with only secondary involvement of the respiratory tract. It is evident, therefore, that the comprehensive term 'congenital laryngeal stridor' can be misleading, since the stridor may be neither laryngeal in site nor congenital in origin. I prefer the less ambitious term 'infantile stridor', which avoids implications and, by inference, draws attention to the need for diagnosis of the cause.

Thackeray wrote of the baby who would 'crow with delight', and it is a common experience to hear a healthy infant make an occasional stridorous inspiration with pleasure or excitement, or, still more commonly, at the onset of a bout of crying. Differentiation between the normal and abnormal is, however, generally obvious: in true stridor the sound is repeated or sustained, though it ranges from a mild purr, easily audible only with deep breathing, to a harsh croak which may be heard outside the room or, indeed, the house in which the child is lying.

Character and Intensity. The most vivid descriptions of stridor in the present series were provided by mothers. They varied from 'crowing like a cock' to 'cooing like a dove'. Between these extremes fell the wheezers and the graters, the creakers and the croakers, and many more, including the child who was thought to have swallowed a whistle. Grunting was a common descriptive term, 'asthma' not unusual, and 'hissing' or 'bubbling in the throat', or even 'a sieving noise', have been applied to describe what was heard. In one case the paradoxical combination of aphonia with stridor occurred.

The character and intensity of the stridor were evidently related to the degree of obstruction of the airway, but bore no apparent relation to the type of underlying anomaly.

Changes in Character. In one patient a 'crow' changed to a 'whistle' at 21 months, and to a 'squeak' a few months later. Less dramatic changes in the sound were usual. Quite frequently the stridor was extremely soft; it could readily be missed by the observer in the first few days of life, but became louder after a variable period of days or weeks. This observation must be set against retrospective estimates of incidence which are based on records of the immediate neonatal period. Only two cases were recorded among 11,076 consecutive live births by Wilson (1952b), but in my experience the incidence is several times higher.

On reaching its peak of intensity the stridor in most cases remained fairly constant for a few months, and then receded gradually. Later it was heard only with crying or excitement, or eventually only in the presence of superimposed respiratory infections, before it was finally lost completely. Over the whole span of the condition, and especially in the later stages, the stridor tended to wax and wane in intensity; usually the exacerbations were

found to coincide with an upper respiratory infection, though this was often a mild one.

Timing. In the large majority of cases stridor was confined to the inspiratory phase of respiration; in only two of this series, both infective in origin, was it audible both in inspiration and expiration.

Beginning of Stridor. In four of every five cases, whatever the cause, stridor was heard initially within a few days of birth, most commonly on the first day. In most of the remainder it was evident for the first time before the end of the second, and in a few the third, week. In this series stridor was heard for the first time three weeks after birth in one infant with a tracheal anomaly; at five weeks in one with micrognathia and in another with paralysis of a vocal cord; at seven weeks in a mongol; and as late as three months in a baby with congenital heart disease.

In the group of cases with congenital laxness or deformity of the epiglottis and supraglottic structures stridor almost invariably began in the first few days, nearly always on the first day. Stridor associated with laryngeal oedema or trauma of the larynx during birth, or with cerebral irritation, also began without delay. Where stridor was due to anatomical aberrations outside the larynx the onset was usually, but not always, immediately after birth. In an important group where stridor was associated with upper respiratory infection the characteristic sound was usually heard soon after birth, but sometimes the onset was delayed for two or three weeks. In other cases (not included in the present review), associated with collapse of a pulmonary lobe or segment, the onset of stridor invariably occurred after the first month of life.

Termination of Stridor. In a small minority of cases stridor disappeared in the first few months, or occasionally weeks, usually with some temporary lesion like laryngeal oedema or paralysis of a vocal cord. In the remainder the period over which stridor persisted bore no apparent relation to the underlying cause, though in cases with chronic upper respiratory infection it tended to last longer. In half the total number stridor had disappeared by the age of 1 year, and in nine-tenths of the total by 2 years. In two mongols it was still present at 5 years. In one child stridor, probably infective in origin, was still audible at 7 years; in another, where the cause was undetermined, it was lost finally at 8 years of age.

The Infant

Towards the end of 1945, when I saw an infant with stridor who died (Table 3, Case 3), I looked for detailed information about the mortality associated with stridor, but was unable to find it. There was a similar dearth as regards associated disorders, complications and sequelae. Evidently attention had been focused too closely on a single aspect of the condition, and on a short period of its natural history, during infancy, when an accurate general assessment may be impossible. The survey which was consequently undertaken was planned to be comprehensive, and to collate the results of repeated observations continued at least until the stridor had been outgrown.

Familial Stridor. Two brothers with stridor and micrognathia were reported by Schwartz (1944); Finlay (1949) described one family of three siblings with stridor. In the present series a history of stridor was obtained in five families (Table 1).*

TABLE 1
FAMILIAL STRIDOR

Family	Birth Rank and Sex of Siblings	Stridor	Associated Anomaly
I	Male	Occurred	Epiglottis
	Male	Occurred	? *
	Female (twins)	Occurred	Not determined
	Female (twins)	Absent	
II	Female	Occurred	Epiglottis
	Male	Occurred	? *
	Male (cousin)	Occurred	Cardiac malformation
III	Male	Occurred	Not determined
	Male	Occurred	? *
	Female	Absent	
IV	Male (died)	Occurred	? *
	Male	Occurred	Epiglottis
V	Female	Occurred	? *
	Male	Absent	
	Male	Occurred	Mental defect

* Patient not seen while stridor was present.

The first family showed an additional and puzzling feature. The two eldest children had presented with stridor and opisthotonos, a combination which is not unusual in infancy (Fig. 2), though in these two patients the opisthotonos was extremely pronounced. One of the twins had stridor but no opisthotonos; the other had marked opisthotonos but no stridor, and stridor was not produced on flexing the head. In neither twin was clinical and radiological examination successful in demonstrating the cause.

In the five families recorded there were 14 siblings, of whom 11 had stridor. In no instance was consanguinity of the parents admitted. One first cousin was also affected, but the results of enquiries about other relatives were unsatisfactory and unproductive. The number of siblings with stridor is

* Some of the patients in this group were examined only after the stridor had ceased, and no diagnosis could then be made. They were sent for to be examined, because of the suggestive history obtained when another member of the family was referred for an opinion.

high enough to suggest that a familial incidence has previously been overlooked. Possibly there is a genetic factor concerned, but further details of families with stridor, and opportunities for earlier diagnosis, are necessary to settle this point.

Sex Incidence, Birth Rank, Abnormal Pregnancy and Birth. In this series there was a preponderance of males with stridor, in the proportion of five boys to three girls, which was more or less uniform in each of the aetiological groups. There was no apparent relationship between stridor and birth rank. Abnormal pregnancy preceding the birth of an infant with stridor was rare; the number of cases with abnormal labour appeared to be rather high, but the data are incomplete.

Birth Weight. The birth weights of 72 infants with stridor were compared with those of a group of unselected infants. For this purpose the figures for all live births (with known birth weights) in Bristol during 1951 were taken. Owing to the preponderance of males with stridor it was necessary to compare the sexes separately in the two series. The comparison is shown graphically in Fig. 1.

A preliminary examination, including both males and females, showed the birth weights to be significantly higher in the group of infants with stridor than in the group of unselected cases. Thus, with an arbitrary line drawn at 7 lb., it was found that 22% of the stridor cases fell below it, compared with 36% of the unselected cases; this difference exceeds twice the standard deviation and is therefore significant. On separating the sexes it became evident that the pattern of weight distribution in the males determined that of the whole series. Thus, only 13% of male infants with stridor fell below 7 lb., compared with 30% for males in the unselected series, the difference from unselected males being even more significant statistically.

The unexpected discrepancy between males and females as regards weight distribution is brought out clearly by the following figures:

TABLE 2
STRIDOR CASES

Birth Weight	Males	Females
Under 7 lb. ..	13%	38%
7-8 lb.	48%	31%
8 lb. or over ..	39%	31%

The number of infants whose birth weight fell within the accepted definition of prematurity (5·5 lb. or less) was six (8% as compared with 6% in the unselected series). Of these four were females, a finding which emphasizes the high incidence of females in the weight group 5-6 lb., the difference as compared with the group of unselected females being statistically significant even with the small number of cases available.

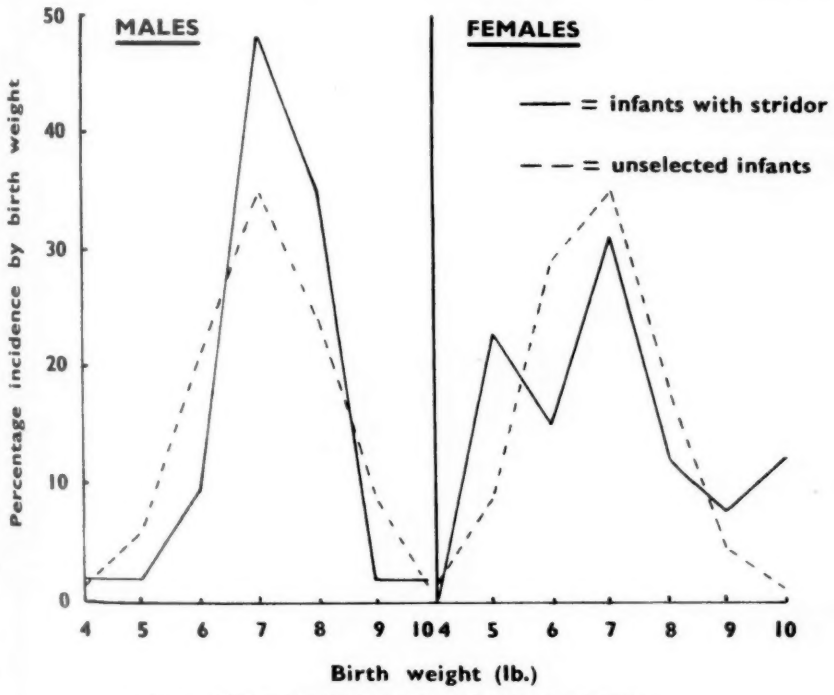


FIG. 1.—Birth weight distribution: sex disparity in stridor cases.

Examination of the aetiological groups of which the stridor series is composed failed to reveal any explanation for these observations.

Associated Congenital Physical Anomalies. In two infants the important presenting feature was a meningo-myelocoele, and stridor was incidental. Both died, one at a day and the other at 3 months, having exhibited marked and persistent stridor and opisthotonos. No abnormality of the respiratory tract was found at necropsy, and it was considered that the stridor was attributable to central nervous dysfunction.

In another infant a moderate degree of talipes equinovarus was present. One other had polydactyly with six digits on each foot and hand.

In six infants with stridor (including two mongols) a congenital cardiac malformation was diagnosed (one with pulmonary stenosis, and five with a septal defect). Paralysis of the vocal cords was not seen in any case, the heart was not grossly enlarged, and no vascular anomaly was demonstrated radiologically which might account for the stridor. It was therefore concluded that in these cases stridor was not caused by a cardiovascular anomaly. In a seventh case the heart was grossly enlarged, and the left vocal cord was paralysed intermittently; it was considered that in this infant the stridor was secondary to the cardiac anomaly.

In this series, therefore, congenital cardiac malformations appeared to be unduly frequent, though the incidence of other physical anomalies was not high.

Mental Condition. Three of the infants with stridor were mongols; two with congenital heart disease and one with stenosis of the larynx.

No fewer than 16 other infants with stridor were mentally retarded. Mental retardation may be difficult to diagnose at a single examination in early infancy, and in some cases a long period of observation was necessary to establish the condition. In eight cases the retardation was severe, and in eight moderate. Clinically the majority showed no abnormality of the nervous system other than the primary failure of mental development, though two were also spastic. In some the larynx, epiglottis and neighbouring structures were abnormal, but in many they appeared normal.

The remaining cases with stridor appeared to develop normally as regards mentality, and exhibited no more than the usual range of variation in the age of their attainments. Neuromuscular control and reflexes also developed normally.

In six of the infants with normal mentality electro-encephalograms taken in the first year of life indicated a normal, or even slightly advanced, degree of development and maturity. It was surprising to find, however, that in two other children, who were mentally defective and have been included in the preceding group, the electro-encephalogram was also normal. Electro-encephalographic examination appears, therefore, from these few cases, to be of no diagnostic value in the early assessment of mental development.

Miscellaneous Conditions. It was long ago suggested that infantile stridor might be due to neuromuscular incoordination, and other evidence of incoordination was therefore sought. An example. was found in an infant with marked mental retardation and spasticity, who had severe stridor and also intermittent achalasia of the cardia. One other patient had hypertrophic pyloric stenosis. It may be added that, though some of the patients in this series are still too young to talk, only one of the older children has developed a stammer.

Rickets, which was of mild degree, was found only once in the present series. In a considerable proportion of the mothers, and in a few infants with stridor, a blood Wassermann reaction was carried out and was invariably negative.

Allergic disorders were rare. One patient had infantile eczema; the sister of another had eczema and came of an asthmatic family, and in two other families asthma also occurred.

One child had moderately severe sequelae of rhesus incompatibility. Another developed convulsions for which no cause was found.

Feeding Difficulties. About half the infants with stridor had some difficulty in feeding, though in very few was this serious enough to retard the rate of increase in weight. A few infants took an unduly long time to feed, but many fed reasonably quickly despite obvious difficulty in breathing while sucking. In a small number frequent choking occurred with feeds; many more vomited during, or soon after, feeding. Apparent difficulty in swallowing was usually abolished with the change over from liquid to solid feeding; but in a small number the reverse applied and swallowing difficulties began only when weaning was started.

There was no evident correlation between feeding difficulties and epiglottic anomalies.

Respiratory Complications. In an infant already labouring under difficulties in breathing, superimposed respiratory infection, with the consequent accentuation of these difficulties, is very quickly noticed. For this reason it is not possible to compare validly the incidence of upper respiratory infections in infants with or without stridor. The majority of my patients did suffer from frequent upper respiratory infections, but it was impossible to decide whether this is or is not significant.

There was, however, one clearly significant feature, the frequent association of stridor with 'snuffles'. In eight cases stridor was first noted at the same time as snuffles appeared; in a further five cases stridor developed within a few days after the onset of snuffles. This suggests a possible connexion between the two conditions, which will be discussed later.

As regards lung infections, there appeared to be a real increase in incidence among the stridor cases. Omitting those patients who died with a pulmonary infection (see next section), it was noted that in nearly one-third of the remainder frequent lung

complications occurred. These included bronchitis, bronchopneumonia and pulmonary collapse.

Deformities of the Chest Wall. These may be described here. With respiratory obstruction there is frequently some retraction of the ribs and soft tissues of the neck and chest wall on inspiration (Fig. 2). It is worth repeating the observation (Holinger and Johnston, 1950) that the site of such retraction (high or low respectively) does not indicate the site of the obstruction, for respiratory obstruction in the larynx may cause inspiratory indrawing of the tissues of the neck, chest wall, and even the upper abdomen. The extent of the indrawing is apparently related only to the inspiratory effort evoked. In its milder forms such recession was seen in most infants with stridor, and in its more marked forms in a few.

FIG. 2.—Opisthotonos and inspiratory retraction of chest wall in an infant with stridor.

I have attempted to assess the type and permanence of the chest deformities which may develop in cases of stridor. It is admittedly difficult to draw the line between normal and mildly abnormal (Naish and Wallis, 1948), but in 15 cases it was judged that significant Harrison's grooves, and in three sternal deformities, were produced; in a further three cases the lower ribs were markedly splayed out, and in two others the chest wall was irregularly deformed. These figures cannot be strictly compared with those of Naish and Wallis, whose cases and controls were all 5 years old or more, but the incidence of early chest deformities is undoubtedly higher than would be expected in otherwise normal subjects. In none of these cases was there any evidence of rickets.

There has been no conclusive answer to the question as to whether continuous indrawing of the chest wall in early life produces deformities which remain permanently (Clerf, 1950). Fig. 3 shows the deformed chest in a boy aged 6 years who had stridor in infancy, complicated by repeated pulmonary infections; but in only two of the children in this series did more than a minor degree of deformity persist after the first few years. In these two cases lung infections had occurred frequently, and probably played an important part in producing permanent deformity.

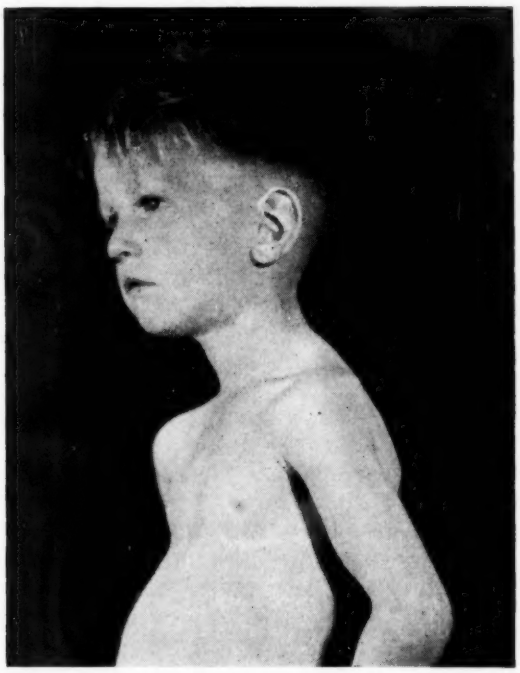


FIG. 3.—Marked chest deformity in a boy aged 6, following stridor in infancy and repeated respiratory infections.

Fatal Cases. The reputedly benign course of infantile stridor still erroneously continues to be stressed, though occasional fatalities have been referred to in the literature. I have been unable to find any survey of fatal cases in the published reports, with the exception of White Franklin's (1952) reference to three deaths in 30 cases. The deaths in the present series are recorded in Table 3.

TABLE 3
DEATHS IN CASES OF STRIDOR*

Case	Age at Death	Necropsy	Cause of Stridor	Larynx at Necropsy	Associated Conditions
1	1 day	Yes	Central nervous dysfunction	Normal	Meningo-myelocoele
2	2 days	Yes	Tracheal compression	Normal	Enlarged thyroid
3	3 months	Yes	Narrowing of airway by vertebra	Slight infolding of epiglottis	Malformation of vertebra
4	4 months	Yes	Central nervous dysfunction	Slight infolding of epiglottis	Hydrocephalus and meningo-myelocoele
5	5 months	Yes	Lax epiglottis	Infolding of large epiglottis	Atrophy of left kidney
6	5 months	Yes	Chronic upper respiratory infection	Developmentally normal	—
7	5 months	No	—	—	—
8	10 months	Yes	Chronic upper respiratory infection	Developmentally normal	Abnormally formed first vertebra
9	1 year	Yes	Central nervous dysfunction	Moderate infolding of epiglottis	Spasticity and mental deficiency
10	1 year	Yes	Lax epiglottis and tracheal collapse	Moderate infolding of large epiglottis	—
11	4 years	Yes	Chronic upper respiratory infection	Diminutive chords	Mongol, cardiac malformation

* An additional case, the brother of an infant with epiglottic stridor (see Table 1, Family IV) is reported to have had stridor from birth and to have died at 3 months from bronchopneumonia, but necropsy was not performed.

In Case 2 sudden death, due to obstruction of the airway by a grossly enlarged thyroid, occurred while preparations for operation were being made. At necropsy the lungs were found to be incompletely aerated; the trachea was compressed antero-posteriorly by the thyroid mass, which encircled both trachea and oesophagus. Sections showed the mass to be a hyperplastic angioma (vascular hamartoma).

In Case 3 stridor was also due to an extra-laryngeal cause, one not previously described. This infant had extreme respiratory distress and stridor from birth. On clinical examination anterior protrusion of an upper cervical vertebra was found, greatly narrowing the pharynx. Tracheotomy relieved the symptoms, but death occurred from subsequent lung infection. At necropsy the first vertebra was seen to be grossly enlarged anteriorly, apparently because of an additional ossification centre; the slight lateral infolding of the small epiglottis which was present was no more marked than is seen in many normal infants.

Case 1 (Fig. 4) and Case 4, with serious developmental errors of the central nervous system, but no anatomical abnormality of the respiratory tract, are important in that they confirm the hypothesis that dysfunction of the nervous system can produce stridor. Case 9 falls into the same category. Though moderate lateral infolding of the epiglottis was seen on laryngoscopy at the age of 1 year, and confirmed at necropsy (Fig. 5), this deformity had not been present at 6 months. It was not, therefore, causative but secondary.

In Cases 6 and 8 also stridor occurred in the presence of a normally developed larynx and respiratory tract, and was evidently due to thickening of the mucosa associated with chronic infection. Similarly, in Case 11, though the vocal cords were remarkably small, no developmental cause for stridor

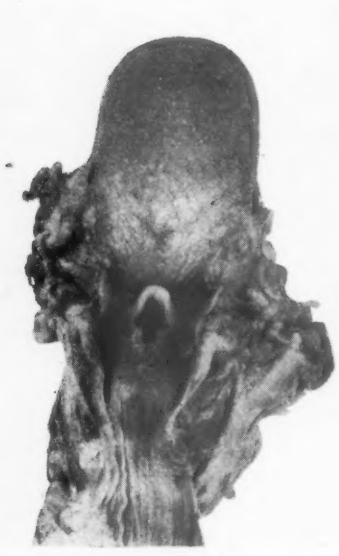


FIG. 4.

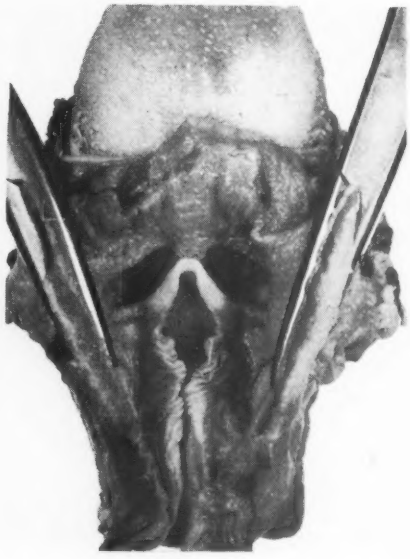


FIG. 5.

FIG. 4.—Normal larynx in an infant 1 day old, with meningo-myelocoele and marked stridor.

FIG. 5.—Infolding of lateral epiglottic margins in 1-year-old girl with mental defect, spasticity and stridor. The epiglottic deformity developed after the first six months of life.

was found, but sections of the mucosa at various levels in the pharynx and larynx showed considerable infiltration and thickening due to chronic infection.

Cases 5 and 7 were classical examples of 'congenital laryngeal stridor', with no apparent abnormality except the flabby epiglottis which was drawn into the larynx with each inspiration. Case 10 was similar, though during life a degree of tracheal collapse, demonstrated radiologically, had suggested the diagnosis of tracheomalacia. No tracheal anomaly was found at necropsy, and it is evident that the tracheal distortion was produced by violent efforts at overcoming the obstruction when the lax epiglottis was drawn into the larynx.

In eight of the nine cases surviving beyond the immediate post-natal period, death occurred from respiratory infection. These fatalities emphasize the seriousness of infections in infants in whom the respiratory tract is already functioning at a disadvantage.

The Upper Respiratory Tract

Upper respiratory tract abnormalities occurred in the majority of infants with stridor, and are grouped according to site, with one additional group in which there was widespread involvement of the upper respiratory tract by infection.

Micrognathia. The part played by micrognathia in the production of stridor by permitting displacement of the epiglottis has been stressed by Schwartz (1944). In the present series micrognathia was present in five infants with stridor, and in three of these was only of moderate degree. In four of the five laryngoscopy was done. In one the lateral edges of the epiglottis were markedly rolled in and the whole structure was drawn down during inspiration. In two others the epiglottis was drawn in with inspiration, though it was normal in size and shape. These three cases are consistent with Schwartz's hypothesis. In the fourth, however, the larynx appeared completely normal throughout respiration, and stridor persisted even when the epiglottis was grasped and held in position.

Vertebral Anomalies in the Pharynx. Because of the fatal case with stridor due to a vertebral anomaly (Table 3, Case 3) attention was particularly directed to the cervical vertebrae of all infants with stridor. An anomaly of fusion in the first cervical vertebra was found at necropsy in one other case (Table 3, Case 8), but it had no appreciable effect on the size of the vertebra or the calibre of the air passages.

On routine palpation of the posterior wall of the pharynx, in a few infants a moderate protrusion of the first cervical vertebra was felt, and in several a less pronounced protrusion, which may have narrowed the pharynx to a significant degree. Radiographs of the vertebrae often demonstrated the same prominence, evidently due to the ossification centre in the anterior arch of the atlas which is occasionally present at birth (Caffey, 1950). I have not, however, been able to satisfy myself that this minor variant of the normal does, in fact, play a part in producing stridor.

Epiglottis. In a little more than one-third of the cases examined the epiglottis appeared completely normal in movement, size and shape. Even in some of the cases with an epiglottic abnormality, however, it was not considered that the stridor was primarily due to this anomaly, or was necessarily produced by the epiglottis. In several instances the latter observation was confirmed by grasping the epiglottis at laryngoscopy and observing that the stridor did not cease.

SHAPE. Abnormalities of shape varied considerably: the epiglottis in different cases was broad at the end, flattened out or wedge-shaped; in others the lateral edges appeared rolled or folded in. I agree with Wilson (1952b) that these variations in shape are not a cause of stridor: they appear to be unimportant variants of the normal, which may also be seen in infants without stridor.

In those cases, however, where the epiglottis is markedly folded back on itself, occasionally in association with a deep pyriform fossa, the abnormally shaped epiglottis in infancy probably does give rise to stridor.

SIZE. Stridor may be produced at the epiglottis if it is greatly enlarged, whether intrinsically or secondarily (by oedema or thickening).

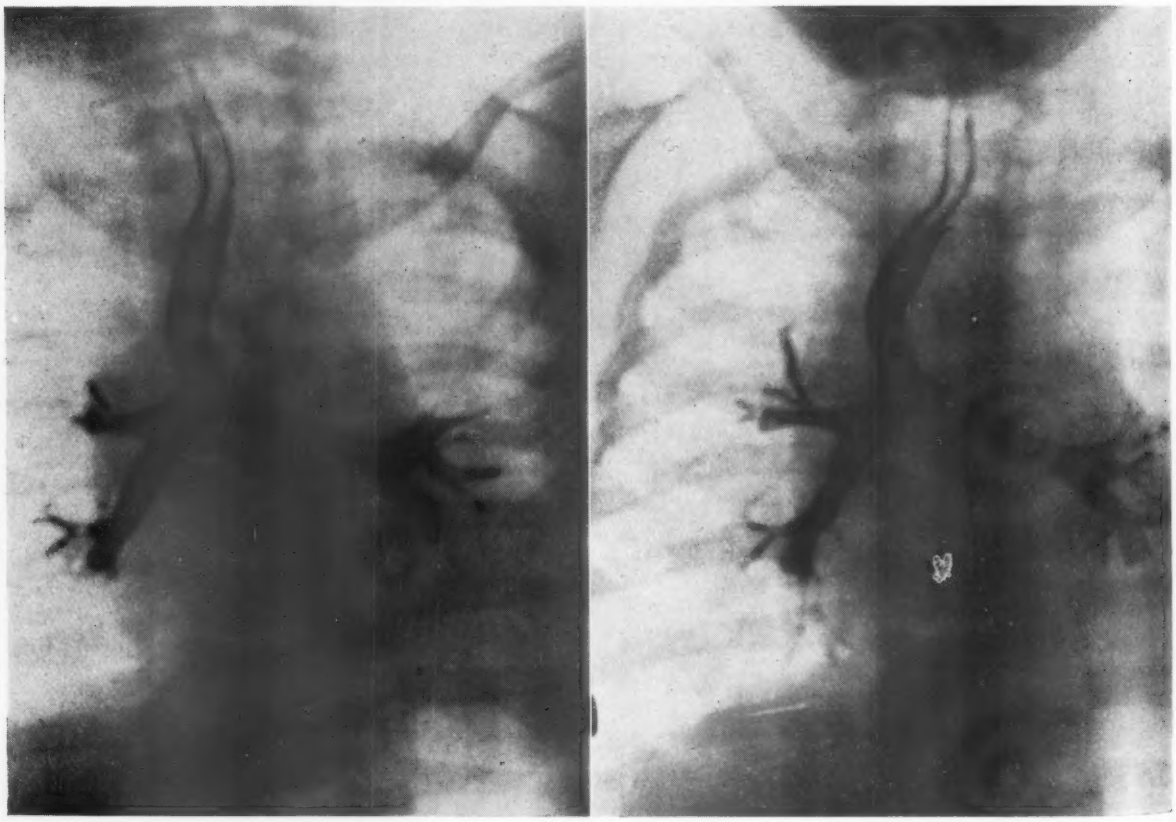
In some cases, where the onset of stridor was associated with upper respiratory infection, the epiglottis (in the early stages, it is important to note) appeared swollen and oedematous. In two of these, which were treated early with antibiotics and were examined at short intervals, the oedema, enlargement and stridor were observed to recede synchronously; at the same time the epiglottis became firmer, and was no longer drawn into the larynx with each inspiration. In the more chronic cases, however, even when oedema and swelling disappeared, the epiglottis continued to be drawn in on inspiration.

MOVEMENT. From the observations made it was concluded that 'sucking in' was the most important epiglottic feature in the production of stridor.

This phenomenon is apparently produced in one of two ways. In the first and smaller group it appears that a relative increase in the force of the air-current is responsible for the 'sucking in'. Such an increase would be expected if the airway is narrowed for any reason, while the total volume of air passing remains

FIG. 6.—Radiograph showing persistent anterior indentation of subglottic region (confirmed by bronchoscopy).

FIG. 8.—Radiograph showing excessive tracheal 'bowing'.



(*a*) (*b*)

FIG. 7.—Tracheogram in (*a*) expiration, (*b*) inspiration, showing inspiratory laryngeal collapse.

undiminished. Narrowing of the area of cross-section of available space in the airway must occur if the epiglottis is disproportionately large, and a primary enlargement was in a few cases considered to account for the sucking in. In patients with extra-laryngeal narrowing of the airway a similar effect may be produced; an example was a case with tracheal collapse, where the epiglottis, though small and firm, was drawn into the larynx on inspiration.

In the second and larger group of cases, however, no anomaly beyond an excessive flabbiness of the tissues was demonstrated. This is apparently due to an exaggeration of the normal characteristics of the infant larynx, as compared with that of the adult.

Larynx. In four patients with stridor due to a primary intra-laryngeal anomaly the following conditions were found. In one there was oedema of the laryngeal mucosa, which persisted for a few weeks. This infant produced a tremendous 'crow' on inspiration, and was cyanosed and distressed from a few hours after birth; the oedema and stridor subsided concurrently. In one newborn infant an abnormal, swollen left arytenoid was found. In another (a mongol) the larynx was stenosed, an association which has previously been described (Bonham Carter and Lovel, 1951). In the remaining case, with aphonia as well as stridor, a persistent indentation in the immediate subglottic region was seen on radiography (Fig. 6) and confirmed by bronchoscopy, though its nature was not determined.

In two other infants unilateral vocal cord paralysis was observed. In one it was associated with birth trauma. In the other it was apparently due to involvement of the recurrent laryngeal nerve by gross cardiac enlargement (see p. 426).

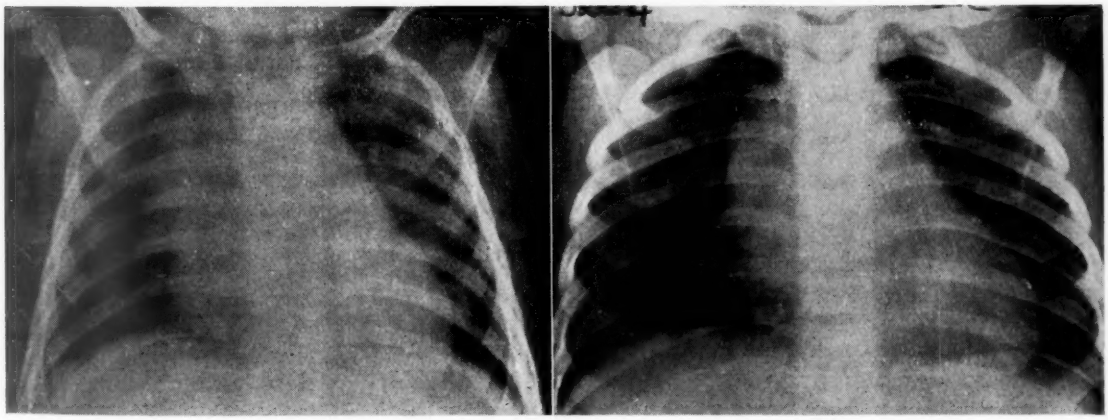
Trachea. Intrinsic defects were first considered.

INTRINSIC DEFECTS. In three cases inspiratory tracheal collapse was the only anomaly demonstrated (Fig. 7). In one superficially similar case the collapse was considered to be secondary and not primary (see p. 429).

In a fourth child there was a marked degree of tracheal 'bowing' (Fig. 8) which persisted during the first three years of life; stridor also ceased at the same age. Bending of a tube through which air is passing has an obstructive effect similar to that produced by narrowing, and it was concluded that the bowing in this case was productive of stridor. In several other infants with stridor a lesser degree of bowing was seen, and a minor degree may be observed in tracheal radiographs of normal infants. The case described, however, was the only one in which the bowing could not be annulled by full extension of the infant's head, and was considered so extreme a variation from the normal as to be pathological.

PRESSURE BY ANOMALOUS ARTERIES. In one patient with a vascular ring the diagnosis was made from the radiological evidence of distortion and constriction of the trachea and oesophagus. In two others, with an aberrant left subclavian and an anomalous innominate artery respectively, the radiological diagnosis was confirmed by angiography (Apley, 1949).

THYROID. A case of thyroid enlargement with stridor due to compression of the trachea has been described earlier. It is, perhaps, surprising that the thyroid is not a commoner cause of tracheal obstruction, since in the newborn infant thyroid tissue may extend between the trachea and oesophagus and the main part of a goitre may even lie behind the trachea (Hamne, 1946). Moreover, if the treatment of goitre with iodine or with thiouracil in adult women is continued during the last weeks of



(*a*) (*b*)

FIG. 9.—Chest radiographs showing large thymus in a child at (*a*) 4 months of age when stridor was present, and (*b*) 16 months when stridor had ceased. No compression or distortion of the trachea could be demonstrated.

pregnancy, the newborn infant may present with thyroid enlargement and consequent stridor, and death has occurred (Page, 1953).

THYMUS. In several infants a large thymic shadow was seen on radiography (see Fig. 9) and radioscopy, but in none could distortion or compression of the trachea be demonstrated, and stridor was therefore not attributed to thymic pressure in any of the cases in this series.

Upper Respiratory Infection. In eight infants stridor and snuffles developed simultaneously, in most cases within the first 48 hours of birth; in five others snuffles was followed by stridor within a few days. In some infection of the skin and/or conjunctivae was noted at the same time.

In the infants in this group who were examined in the early stages the whole upper respiratory tract, including the epiglottis and larynx, was seen to be involved in an inflammatory process of which snuffles was only part.

Stridor with No Apparent Upper Respiratory Abnormality. The only cases excluded from the present series were those with stridor due to pulmonary collapse. In 10 of the 80 cases which form the material of this survey investigation was incomplete, in most instances because the patient was first seen when stridor had completely or almost completely ceased.

In 15 fully investigated cases, however, there was no demonstrable upper respiratory abnormality, or there was an abnormality whose significance in the production of stridor was doubtful. Included in this group were cases with a minor degree of tracheal bowing, or with a moderate anterior vertebral prominence in the pharynx. In three of seven patients with congenital heart disease, and in half the 16 mentally defective children, no upper respiratory abnormality was found.

Discussion

Stridor in infants is an expression of many disorders, differing widely in aetiology. There is clearly a need for further series of unselected cases to provide larger numbers for analysis in each aetiological group. Until these become available the significance of the observations described in this paper on familial incidence, the high proportion of males and the sex discrepancy in birth weights cannot be finally assessed.

The complications, sequelae and high fatality rate recorded for the first time in the present series indicate the need for further long-term surveys. The value of follow-up observations is further exemplified by the high incidence of mental deficiency and of congenital heart disease; if assessment is restricted to the first examination, or even to the period of infancy, many of these conditions remain unrecognized.

Diagnosis. Since stridor is merely a manifestation of a disorder, which may be mild or extremely grave, the precise underlying cause should be sought in every case. The investigation of an infant with stridor calls for various ancillary methods of examination, in addition to clinical assessment.

Chest radiography and radioscopy are essential, especially in the diagnosis of pulmonary collapse, which may be difficult or impossible to detect in the infant by clinical means alone. These methods are essential also in the diagnosis of congenital cardiac and vascular anomalies, which may cause stridor. The role of a large thymus in the production of stridor should not be assumed unless it produces demonstrable pressure effects.

The upper respiratory passages can be clearly visualized by radiography, and lateral views are especially useful. If doubt exists radiography may be repeated with the instillation of a small quantity of opaque medium in the trachea (see Fig. 7) followed by its prompt removal. This method, though rarely necessary, appears to be safe.

Direct laryngoscopy is necessary for diagnosis in every case. The potential danger, that in infectious cases obstructive oedema may ensue, has not been encountered in this series. To obtain the necessary information regarding mobility, as well as other features, the tip of the laryngoscope should be placed first in the vallecula and then below the epiglottis.

The above methods, employed to demonstrate abnormalities in the respiratory tract itself, are more likely to be productive if they are used early. The proportion of diagnosed cases falls proportionately with delay in investigation, and with delay diagnosis may also be confused by the observation of changes which are secondary.

Even with full and early investigation, however, in a proportion of patients no abnormality is demonstrated in the respiratory tract, and these cases form a most interesting group. It is, of course, conceivable that minor anatomical abnormalities may fail to be detected by the methods in use at present. Nevertheless, an abnormality sufficiently gross to produce stridor might be expected to be apparent, and the absence of any abnormality of the respiratory tract has in some cases been confirmed at necropsy. It is therefore necessary to seek elsewhere for a cause, and the central nervous system appears the most likely source.

Assessment of nervous function is, unfortunately, crude, and minor degrees of dysfunction may be

undetectable. Electro-encephalography for this purpose was found to be unhelpful, and the most satisfactory method available is long-term clinical observation with particular attention to mental and neuromuscular development. Even so, in a small proportion of cases no evidence of abnormality other than transient stridor is found; in these it is tempting to speculate that stridor is produced by temporary nervous dysfunction.

Nervous Dysfunction and Stridor. In half the cases of disorder of the central nervous system in which the larynx was examined an epiglottic or laryngeal abnormality was found; there was, therefore, in this group a high incidence of these abnormalities, as compared with normal infants. The abnormality was usually one of movement, i.e., the epiglottis and arytenoids were drawn into the larynx on inspiration, just as occurs with the so-called primary lax epiglottis; in a few cases the epiglottis was also markedly inrolled, and in one it was folded transversely on itself.

In one infant, with clinical signs of marked cerebral irritation from birth, respiratory difficulty and stridor began at the same time. They gradually receded after the signs of intracranial disturbance disappeared, finally to be lost in the fifth month. Laryngoscopy and other examinations were repeated, but no abnormality could be demonstrated in the respiratory system. This case probably corresponds to those where intracranial damage, producing stridor *inter alia*, has been confirmed at necropsy (Thomas, 1921).

In two fatal cases with meningo-myelocoele and paralysis of the legs and anal sphincter, clinical and post-mortem evidence could be collated. In the first (Table 3, Case 1) the respiratory tract appeared normal in all respects at necropsy; nevertheless, during life, with each inspiration the epiglottis was drawn into the larynx so forcibly as to obstruct the airway almost completely. Moreover, when the epiglottis was grasped with forceps the stridor was abolished. In the second (Table 3, Case 4) no abnormality of the respiratory tract was found during life or after death. In these two cases the absence of an anatomical abnormality of the respiratory tract makes it reasonable to attribute the stridor to the gross neurological anomalies, even though detailed study of the central nervous system was not feasible.

In Case 9 (Table 3) the brain at necropsy appeared macroscopically normal, though the child had been mentally defective and spastic, and had had achalasia of the cardia. The only noteworthy feature in the upper respiratory tract was moderate infolding of the lateral epiglottic margins; the stridor, like the achalasia, was therefore considered to have been produced by neurological dysfunction. Another infant with a clinically normal respiratory tract was blind and spastic and mentally defective.

In the above cases the cause of stridor could reasonably be attributed to nervous dysfunction. In a larger number of children with mental defect, but unaccompanied by gross physical anomalies or spasticity, stridor also occurred. In these the evidence justifies only a statement that the two conditions are frequently associated, though there may conceivably be a causal relationship similar to that already considered.

Upper Respiratory Infection as a Cause of Persistent Stridor. Observations on the association between stridor and upper respiratory infection, and the sequence of events in these cases, have previously been described. It is suggested that infection can produce dysfunction and secondary deformities in the larynx which may, I think erroneously, be considered as primary.

The association observed between upper respiratory infection and stridor would be expected from various factors which apply particularly to the infant. They have been clearly summarized by Holinger and Johnston (1950). The first is the small size of the infant larynx. The glottic orifice of the newborn infant has a cross-sectional area of 14 sq. mm. Oedema to a depth of 1 mm., which would give rise to hoarseness in the adult, will reduce this area to 5 sq. mm. and give rise to respiratory difficulty and stridor in the infant. The second factor is the arrangement of the mucosa and sub-mucosa. The mucosa, while firmly attached to the posterior surface of the epiglottis, is loosely attached on the anterior surface and along the aryepiglottic folds (Lederer, 1946); inflammatory extravasation and oedema will accordingly be localized mainly to the front and sides of the epiglottis, and will cause its lateral edges to curl in and the tip to be bent backwards. From the changes seen in infants who were examined frequently from the earliest stages it appears that if these induced deformities are maintained for a sufficient length of time they may persist even after the inflammatory reaction has subsided.

In a survey of 30 infants with stridor Bowman and Jackson (1939) attributed the stridor in two to hypertrophic laryngitis. Stridor beginning with acute laryngitis may therefore persist if the laryngitis becomes chronic; but the observations recorded here suggest that even when laryngitis has resolved stridor may persist. It does so evidently because of persistent deformity of the epiglottis and neighbouring tissues which develops while a transient infection is present.

Primary and Secondary Abnormalities of Larynx and Epiglottis. It is evident that congenital anomalies of the larynx do not, as was once believed, account for all, or even for a large proportion of cases of infantile stridor. Wilson (1952b) found a normal larynx in five infants out of 10 with stridor. Among the present series, in one-third of the patients fully investigated the larynx and epiglottis appeared completely normal; of the remainder, in only 22 was the abnormality considered to be congenital and the primary cause of stridor. In three cases with stridor which came to necropsy White Franklin (1952) reported a normal larynx in all three; in two of my 10 cases at necropsy an epiglottic malformation considered to be the primary cause of stridor was found, in four there was no abnormality, and in four the changes observed were evidently slight and secondary or unrelated. Thus in only a small proportion of the total, either clinically or at necropsy, is stridor attributable to a primary anomaly of the larynx.

The number of cases in which stridor is considered to be due to a primary laryngeal or epiglottic abnormality dwindles considerably when other factors are carefully reviewed. It is of interest, therefore, to consider the possibility that abnormalities of the epiglottis and remainder of the larynx might always be secondary.

The high incidence of epiglottic and laryngeal abnormalities in association with nervous disorder has been indicated. In these cases it is conceivable that the abnormality, particularly of movement, may have been secondary. On the other hand, in half the cases with a disorder of the nervous system there was no demonstrable abnormality in the upper respiratory tract.

Similarly, in those patients in whom an extra-laryngeal cause of stridor was present in the upper respiratory tract (micrognathia, arterial or tracheal anomalies), epiglottic abnormalities were seen in one-third of the cases examined. These abnormalities varied from inrolling of the lateral edges to complete inspiratory collapse, with inspiratory indrawing of the epiglottis and aryepiglottic folds as the constant feature.

In infants with widespread upper respiratory infection, occurring soon after birth, changes in the epiglottis and surrounding structures, which were evidently secondary, occurred and persisted.

It is concluded from the above discussion that in some infants abnormalities of the epiglottis and surrounding structures are primary developmental aberrations, which may be merely associated with developmental defects elsewhere. In other cases similar changes develop secondarily to nervous dysfunction or to infection in the upper respiratory tract.

Diagnosis of the primary cause of stridor is apparently complicated by the inter-relationships described, but in the large majority of cases the difficulties can be resolved. To assess the part played by primary anomalies of the upper respiratory tract, or by neonatal infection, the appropriate investigations must be undertaken early in the natural course of the disorder. Early exclusion of these conditions is suggestive of a primary extra-respiratory cause for stridor; but the diagnosis is contingent on early, and often long-continued, observation of the patient as a whole.

Classification. A difficulty in any aetiological classification of infantile stridor is that more than one presumptive cause may be found in any individual case. Thus, two or three components of the triad—epiglottic deformity, chronic upper respiratory infection, nervous disorder—frequently occur together. A single deviation from the normal may produce a pathological response, such as stridor; it may, however, fail to produce untoward effects unless the resulting disturbance is reinforced by some additional anomaly.

The disparity between the larynx of one healthy infant and another is evidently due to variations in the normal developmental processes which have been described by Negus (1949). Primary laryngeal stridor may be produced by an extreme degree of variation; but, even where stridor is secondary, it must depend to some extent on the structure of the larynx in which changes are potentiated. There is a narrow margin for structural or functional variations in the infant's larynx, and stridor may be produced by a wide variety of laryngeal and extra-laryngeal disorders. In consequence, the detection of a laryngeal abnormality does not necessarily indicate a primary laryngeal cause for the stridor.

The classification of stridor into laryngeal and extra-laryngeal groups is, therefore, not wholly satisfactory. An alternative classification into anatomical, functional and infective groups is suggested.

ANATOMICAL. In this, the largest group, the anatomical patency of the respiratory lumen is reduced. In the majority of cases the primary abnormality is in the larynx; but in some it is extra-laryngeal, occurring at any level in the upper respiratory tract.

This group comprises such conditions as micrognathia, vertebral anomalies, epiglottic and laryngeal deformities, laryngeal web or stenosis, crico-arytenoid dislocation, and cysts, tumours, aberrant arteries and thyroid enlargement.

FUNCTIONAL. In this group the functional patency of the lumen is reduced. The primary abnormality may occur in the respiratory tract or in the nervous system.

Examples of the former are tracheal collapse and inspiratory indrawing of the anatomically normal epiglottis. Nervous disorders may be peripheral (affecting the recurrent laryngeal nerve) or, more commonly, central. Included in this group are the rare neonatal tetany and laryngismus stridulus, and developmental and traumatic disorders of the brain.

INFECTIVE. In this group the respiratory lumen is narrowed by inflammatory processes, the effects of which may persist even when the inflammation has subsided.

This group comprises many of those cases in which stridor and widespread upper respiratory infection develop concurrently in the early neonatal period.

Summary

Observations are recorded on 80 cases with stridor developing in early infancy. To determine the natural history of the condition progress was assessed clinically and by ancillary methods for periods up to several years. Attention was directed not only to the sequence of any changes in the larynx, but also to general physical and mental development.

Stridor occurred in 11 of 14 siblings in five families. In the whole series there was a male preponderance, in the ratio of five boys to three girls. The average birth weight of males was significantly higher than that of females with stridor, and of unselected infants of either sex.

In seven cases a congenital cardiac malformation was present, though in only one was it the cause of stridor. Three patients in the series were mongols; 16 others were mentally retarded.

Feeding difficulties occurred in half the total number. Pulmonary complications were frequent. Chest deformities developed in many cases but were almost invariably transient.

Eleven patients died, and in 10 necropsy was performed. Apart from two cases of meningomyelocoele and one of thyroid enlargement, death was invariably due to pulmonary infection.

In the largest group of cases stridor was produced by an anatomical anomaly which impaired the patency of the upper respiratory tract; in the majority of these the anomaly was epiglottic. In a second group stridor was considered to be due to dysfunction of the nervous system. In a third group stridor originated with an upper respiratory infection.

The mechanism of production of stridor in these groups is discussed, with particular reference to primary and secondary changes in the larynx. It is emphasized that in the investigation of infantile stridor it is essential to make early and repeated observations, not only of the larynx and respiratory tract, but of the patient as a whole.

It is a pleasure to acknowledge my indebtedness to many colleagues, without whom this survey could not have been completed. They include Mr. A. D. Bateman and Mr. H. D. Fairman for instruction and advice, and Mr. V. E. Negus and Mr. J. Angell James for helpful suggestions on laryngological aspects; Professor A. V. Neale and Dr. B. D. Corner for allowing me access to some of their cases; Drs. H. J. Johnson, J. M. Sheach and A. C. P. D. Thomson for their cooperation in the radiology of the respiratory tract; Professor T. F. Hewer and Drs. J. Heathcote, C. D. Cross and M. C. H. Dodgson for advice on pathological specimens; and Dr. G. Herdan for help with statistical problems.

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THE RESULTS OF A NATIONAL INQUIRY INTO THE GROWTH OF PREMATURE CHILDREN FROM BIRTH TO 4 YEARS

BY

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In this paper we describe the growth of a national sample of premature children who have been followed up from birth to 4 years and who, throughout this period, have been contrasted with a closely matched group of children born at term. This is the second of three papers about these children; the first (Douglas and Mogford, 1953) described their health, and the third will describe their development and behaviour. Our present aims are as follows:

(*a*) To describe in what ways, if any, the growth of these premature children differs from the growth of their controls: (*b*) to relate any differences that are found to the initial handicaps of the premature children, to the lengths of gestation, to the histories of pregnancy and to the heights and weights of their mothers; (*c*) to show the relative importance of prematurity as a cause of retarded growth in the whole population of young children in Great Britain.

PREVIOUS STUDIES

During the last 30 years many studies of the growth of premature children have been made, but the results are conflicting and it is still not possible to say how far, if at all, these children are physically handicapped in later life. Capper (1928) reported that they were retarded in growth even after the age of puberty; Hess, Mohr and Bartelme (1934) on the other hand found no reliable deficit in stature after 3 years of age. Illingworth (1939) found that a high proportion of the premature children attending an out-patient department were stunted and, in a later paper (Illingworth, Harvey and Jowett, 1950), showed that there is a direct relationship, that is, not limited to those children normally regarded as premature, between birth weight and subsequent physical development. Asher (1946) concluded that many premature children remain smaller than their fellows at least up to the age of 6 years. Drillien (1948) regarded the physical retardation of her sample of premature children as being a reflexion of the adverse environmental conditions associated with prematurity rather than a result of premature birth *per se*. Glaser, Parmelee and Plattner (1950) concluded that premature babies grow faster than mature babies during the first eight months of life and rapidly reduce their initial handicap.

This list of studies could be expanded many times without yielding any more consistent guide to the physical prognosis of prematurity. There appear to be two reasons for this. First, in all studies a relatively large proportion of surviving premature children could not be traced. For example, Capper, even though he enlisted the help of the Viennese police, lost 54% of the children he was looking for, Hess *et al.* lost 75% and Drillien 60%. These great losses would not matter if it were certain that a representative sample of the premature children had been traced. But the type of children found will depend on the channels through which they have been sought: whether, for example, contacts were made mainly through welfare centres or mainly through out-patient departments of hospitals. Moreover, to judge from the experience of the present inquiry, an unduly high proportion of the defective children will be in institutions outside the authorities where they were born, and so will normally be lost to a local follow-up study. Of our 'main survey' sample, only three out of the 13 children who were living in institutions would have been found in the authority where they were born.

The second reason for the failure of earlier inquiries is that prematurely born children were in no instance compared with a suitable control group of heavier children. Thus Glaser, Parmelee and Plattner were content to compare the growth of their children in 1945-50 with Woodbury's norms of growth which were prepared in 1921. Hess *et al.*, in an attempt to eliminate the effects of environment,

tried to compare prematurely born children with their sibs. But only 105 brothers and sisters could be found to match with 250 premature children and they were, of course, often of different sex and always of different age from their matched pairs. Comparisons of growth are only meaningful if made between children of like sex and age, and accordingly Mohr and Bartelme were in fact comparing premature children not with their own brothers and sisters, but with children drawn from other families. In her Edinburgh inquiry, Drillien used as controls one in 10 of the children born in the hospital from which she drew her sample of premature births. But this control group, as she points out, did not allow for the fact that premature children tend to come from the poorer social classes, and it was not clear from her study how much of the retarded growth of these children was to be attributed to a poor environment and how much to prematurity.

NATURE OF THE SAMPLE

In the present study premature children from all parts of the country and from all social classes have been followed up from birth to 4 years and compared with a group of children weighing more than 5½ lb. at birth. These children were enrolled in 1946 when a Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee, with the help of medical officers of health and health visitors throughout the country, investigated all confinements taking place in England, Wales and Scotland during the first week of March in that year (Royal College of Obstetricians and Gynaecologists and Population Investigation Committee, 1948). We have chosen as our sample of premature children all legitimate singletons who were notified to the Joint Committee during the survey week and who weighed 5½ lb. or less at birth. This standard of prematurity is now generally accepted for statistical purposes and has been used in most recent studies of the growth of premature children. For these reasons it has also been used in the present paper, though of course not all children of this weight range were premature in the sense that they were born before term.

Each premature child was paired with another child selected from the remaining legitimate singletons born during the first week of March, 1946, who was of the same sex and place in the family, who lived in the same locality, and whose mother was of the same age and came from a family in the same social group. Owing to the large numbers of children from whom we could draw, the majority of premature children could be closely matched for these characters (see Douglas and Mogford, 1953).

This comparative study of children born prematurely and at term is part of a much larger inquiry into the health, growth and development of a national sample of children. This larger inquiry (which will be referred to as the 'main survey') is mentioned here because it provides figures which allow us to estimate the importance of prematurity as a cause of retarded growth in the whole population of young children. The detailed planning of it has been described elsewhere (Douglas, 1951).

INFORMATION AVAILABLE

We have had considerable success in tracing the children in our sample, as Table 1 shows.

TABLE 1

LOSSES OF PREMATURE AND CONTROL PAIRS IN 1946-50

Type of Loss		Number of Pairs
Unavoidable	Death	173
	Emigration (1946-48)	21*
	Emigration (1948-50)	10*
Avoidable	Refusals	6†
	Untraced	2†
Alive and still in Survey		464
	Total	676

* Alive at time of emigration.
† All known to be alive in 1950.

These figures, however, underestimate the actual loss of information on the children's heights and weights because, for example, not all parents took their children to be weighed and measured at the required time. The extent of these additional losses and our checks on the accuracy of the measurements obtained will now be described.

The survey children were weighed at birth. Subsequently they were weighed and measured when they were 2 years old, and again when they were 4 years and 3 months. The weights were recorded in pounds and ounces, and the standing heights in feet and inches. It was hoped that these measurements would be taken for all the children at approximately the same time, that is to say in March, 1948, and June, 1950. But owing to difficulties in tracing them, some of their weights and heights were not obtained until several months later. In the following analysis we have excluded 2-year-old measurements taken later than June, 1948, and 4-year-old measurements taken later than September, 1950. A further source of loss was that some mothers, although willing to answer questions on their children's health, were unwilling or unable to take them to welfare centres to be weighed and measured. Since we have throughout this study treated our children as

matched pairs, both children of a pair were excluded if information was missing for one of them. It will be seen in Table 2 that the number of pairs lost varies in each year and for each measurement.

TABLE 2
LOSS OF MEASUREMENT DATA

Type of Measurement	Age (yrs.)	Measurements Available for				Total Number of Pairs
		Both Members of Pair	Premature Child Only	Control Only	Neither Member of Pair	
Weight	2	350	52	66	6	474
	4	363	43	47	11	464*
Height	2	375	38	55	6	474
	4	372	43	37	12	464*

* Ten children left the country between 1948 and 1950 (see Table 1).

These losses are considerable, but the figures in Table 3 suggest that they have not introduced any serious bias into the study. This table shows the mean weights and heights of children who were measured but whom we had to exclude because they were paired with others whose weights or heights were unknown. These means are closely similar to the means for children retained in the sample, as will be seen by comparing them with the figures in Table 4.

TABLE 3
MEAN WEIGHTS AND HEIGHTS OF CHILDREN EXCLUDED BECAUSE MATCHED PAIRS HAD NOT BEEN WEIGHED OR MEASURED

Type of Measurement	Age (years)	Premature Children	Controls
Weight (lb.)	2	26·60	28·85
	4	35·53	38·14
Height (in.)	2	32·76	33·76
	4	39·33	40·61

At each age the health visitors were asked to weigh the children without clothes, but it was evident from the answers given in 1948 that this had not always been done. In 1950, therefore, we specifically asked health visitors to state what clothes were worn, and it appeared that one or both members of 162 pairs were weighed when dressed. The mean weight of all the clothed children is 1 lb. greater than the mean for all those weighed unclothed, and accordingly this amount has been deducted from their weights in the following analysis. It was, however, only possible to make this adjustment in the 1950 weights as our information on clothing in the 1948 survey was certainly not complete. We feel, however, that this is unlikely to have reduced the value of the following comparisons because approximately the same number of premature children and controls were weighed with their clothes on, and we are concerned with a statement of means rather than with a description of individuals.

It is notoriously easy to make errors when taking and recording measurements. Accordingly we checked all the very high and very low measurements, referring back to the medical officers of health for verification all weights, heights and weight-height ratios that fell more than two standard deviations from the mean for the main survey sample.

In both surveys there was a tendency for weights and heights to be recorded as even rather than odd numbers. The reason would appear to be that although weights were asked for in pounds and ounces and standing heights in feet and inches, many health visitors gave them to the nearest pound or the nearest inch and, when they had to choose between an odd or an even number, tended to favour the latter. Since the same tendency is found for both premature children and their controls there is no reason to believe that the comparisons made in this paper are invalidated by this peculiarity of recording.

RESULTS

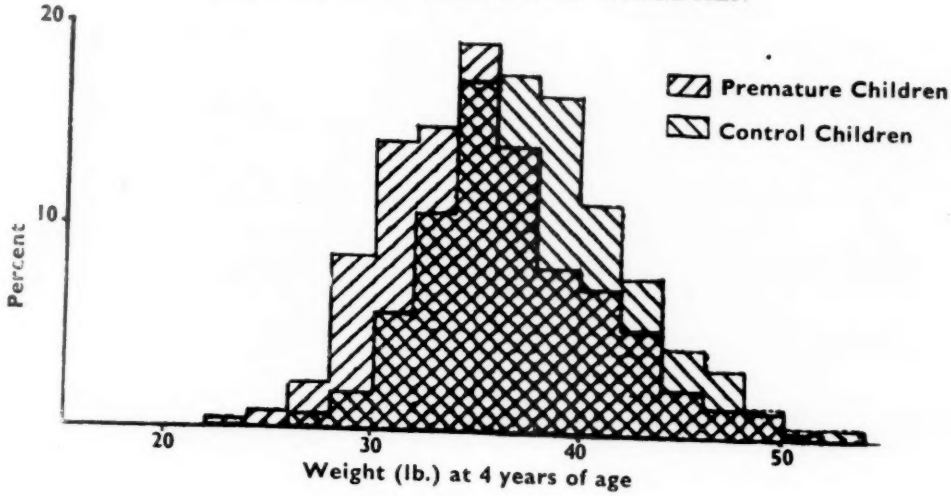
Comparison of Heights and Weights of Premature Children and Controls at Different Ages

There are no significant sex differences in the extent to which premature children lag behind their controls in either weight or height. Accordingly, since the pairs have been matched for sex, data for the two sexes have been pooled in the following analysis.

The frequency distributions of the weights and heights of 4-year-old premature children and their controls are shown in Fig. 1. It will be seen that for both these measurements, the distribution of the premature children lies to the left of the distribution of the controls; that is to say, they are as a group lighter and shorter. The distributions are of the same shape, and there is no suggestion of a concentration of low measurements among a relatively small section of the premature children, the remainder being of normal weight and stature.

It is of interest that premature children of low birth weight appear to be no more stunted in later life than are those who were heavier at birth. Thus 109 of the premature children were 38 in. or less in height at 4 years. Of these, three had weighed $3\frac{1}{2}$ lb. or less at birth, which is the number that would have been expected from the proportion of children of this low birth weight (3·1%) in the whole sample of surviving premature children. The number of surviving children of this weight is small, however, and this observation, which does not fit in with the opinion of many clinicians, needs to be confirmed.

Table 4 gives the average birth weights and the



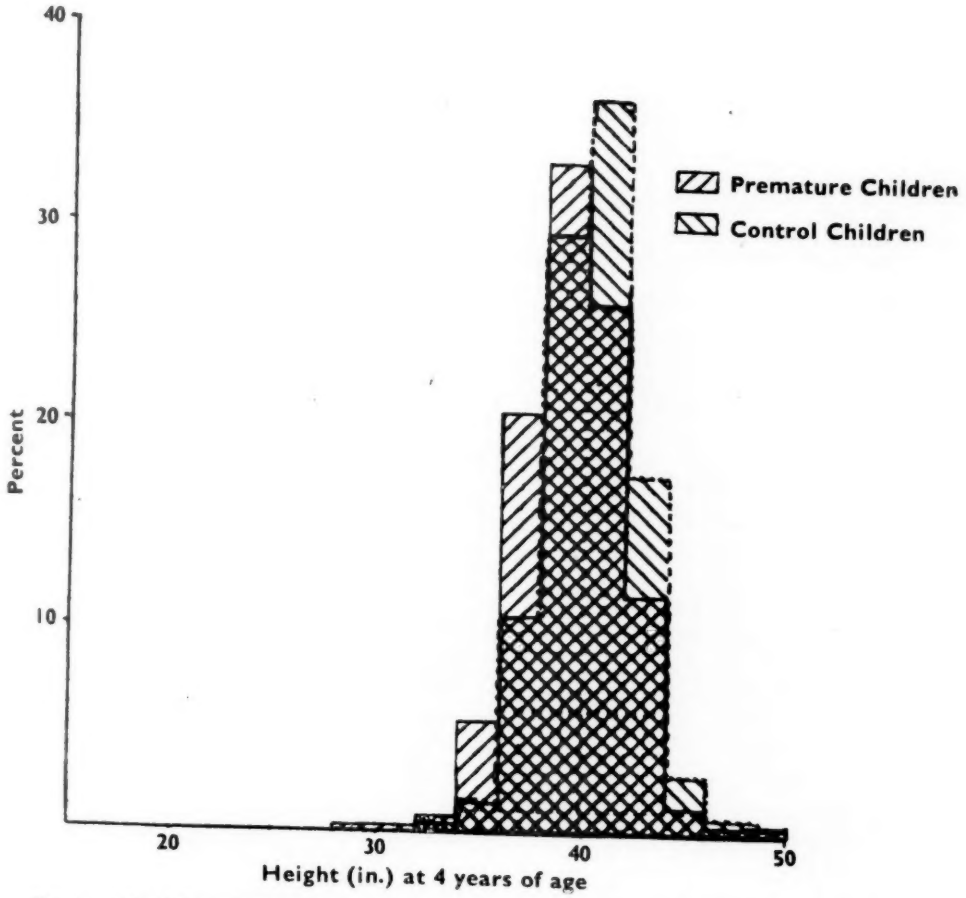


FIG. 1.—(*Above*) Percentage distribution of weights of 4-year-old premature children and their controls.
FIG. 1.—(*Below*) Percentage distribution of heights of 4-year-old premature children and their controls.

average 2-year-old and 4-year-old heights and weights of the premature and control children. We have included in this and subsequent tables 11 premature children of known weight and height who either had birth injuries or congenital abnormalities.

TABLE 4
MEAN WEIGHTS AND HEIGHTS OF PREMATURE CHILDREN AND CONTROLS

Type of Measurement	Age (years)	Premature Children	Controls	Difference	Number of Pairs
Weight (lb.)	At birth	4·91	7·48	2·57±0·05	474
	2	26·24	28·16	1·92±0·23	350
	4	35·37	37·86	2·48±0·34	363
Height (in.)	2	32·46	33·43	0·97±0·15	375
	4	39·39	40·33	0·94±0·15	372

At both 2 and 4 years, premature children are on the average lighter and shorter than their controls; they are approximately 2 lb. lighter at 2 years, and 2½ lb. lighter at 4 years, and at both these ages they are 1 in. shorter. These differences are highly significant. They may be put another way by saying that the weight of the average 4-year-old premature child is equivalent to that of a mature child of 3 years 6 months, and his height to that of a mature child of 3 years 8 months.

It will also be seen in Table 4 that although premature children are significantly less retarded in weight at 2 years than they were at birth, they lose ground between 2 and 4 years, and at the latter age are as much behind their controls in weight as they were when born. The deficit in height, on the other hand, remains constant between 2 and 4 years.

In Table 5 the measurements of the matched pairs have been grouped according to the birth weight of the premature member. Instead of giving separate figures for the measurements of the controls and the premature children, we have, in this and subsequent tables, given the average differences between their measurements. As the controls are in each group on the average taller or heavier, all these differences are positive; for convenience we will refer to them as the height or weight handicaps of the premature children.

TABLE 5
MEAN WEIGHT AND HEIGHT HANDICAPS OF PREMATURE CHILDREN OF DIFFERENT BIRTH WEIGHTS

Handicap	Age	Birth Weight of Premature Child				
		4 lb. or less	4-4½ lb.	4½-5 lb.	5-5½ lb.	All Pairs
Weight (lb.)	At birth	4·20	3·01	2·66	2·16	2·57
	2 years	3·03	2·05	1·74	1·79	1·92
	4 years	2·84	2·22	2·74	2·34	2·48
Height (in.)	2 years	2·30	0·67	0·83	0·88	0·97
	4 years	1·34	0·80	0·92	0·91	0·94

The initially large differences between the weight handicaps of these four groups of premature children have been greatly reduced by the time they are 4 years old, but the smallest children at birth are still on the average the furthest behind their controls at this age. It will be noted that, whereas the premature children of birth weight 4 lb. or less tend to catch up throughout the first four years with their controls in weight and height, those weighing more than 4 lb. at birth catch up during the first two years only and thereafter lose ground in both these measurements.

We have so far considered only the average handicaps of the premature children; it is of practical interest, however, to see what proportion of them have eliminated their initial handicaps at different ages. By the time they are 2 years old, 31% have caught up with or surpassed their controls in weight and 44% have caught up with or surpassed them in height. At 4 years the comparable figures are 36% and 44%. In Table 6 the proportions of premature children who caught up with their controls at different ages have been related to their weight at birth.

TABLE 6
PROPORTION OF PREMATURE CHILDREN ELIMINATING WEIGHT OR HEIGHT HANDICAPS AT DIFFERENT AGES

	Age (yrs.)	Weight at Birth of Premature Child				All Birth Weights
		4 lb. or less	4-4½ lb.	4½-5 lb.	5-5½ lb.	
% who have caught up in weight	2	21·2	34·1	34·4	30·9	31·3
	4	41·9	40·5	32·0	35·9	35·8
% who have caught up in height	2	32·4	57·1	42·0	45·0	44·4
	4	46·9	45·0	41·6	43·7	43·5

It appears that premature children who weighed 4 lb. or less at birth were at 2 years the least successful in eliminating their initial handicaps, but at 4 years they were the most successful in doing so. Although this relationship is not statistically significant, it is noted here because it supports the figures in Table 5 which suggest that the smallest premature children grow the fastest.

Influence of Length of Gestation and Complications of Pregnancy

So far the physical handicaps of premature children have been related only to their birth weight. We will now consider whether these handicaps are also related to the length of the gestation period and/or to the health of their mothers during pregnancy. Owing to the relatively small number of pairs only two lengths of gestation were considered: those

ending more than four weeks before the expected date of delivery and those ending later than this. For the same reason no attempt was made to consider the separate effects of different abnormalities of pregnancy, and we were content to divide the pairs into two groups, those where there was a reason (such as toxaemia, ante-partum haemorrhage or induction) for the premature delivery, and those where there was no reason.

The number of pairs available for this analysis was reduced because our information on the length of gestation and the complications of pregnancy was incomplete. In the original maternity survey these details were not asked for since we were then primarily interested in the functioning of the maternity services and in the costs of childbearing. Two years later, however, when it was decided to undertake the follow-up inquiry into prematurity, we attempted to make good this deficiency from the records of the midwives and maternity hospitals which had cared for our survey mothers. We were more successful in obtaining information than we had hoped but, owing to the incompleteness of some records, a number of pairs have had to be excluded. Thus out of 372 pairs for whom 4-year-old heights were known, 78 were excluded owing to lack of information; and out of the 363 pairs for whom 4-year-old weights were known, 79 were excluded. These exclusions have altered the average height handicap at this age from 0·94 in. to 0·93 in. and the average weight handicap from 2·48 lb. to 2·30 lb.; neither of these alterations is statistically significant. Table 7 shows the average weight and height handicaps of 4-year-old premature children related to the length of gestation and to whether or not there was a reason for premature delivery.

TABLE 7

WEIGHT AND HEIGHT HANDICAPS OF 4-YEAR-OLD PREMATURELY BORN CHILDREN RELATED TO LENGTH OF GESTATION AND ABNORMALITIES OF PREGNANCY

	Reason for Premature Delivery		No Reason for Premature Delivery	
	Born not More than 4 Weeks Early	Born More than 4 Weeks Early	Born not More than 4 Weeks Early	Born More than 4 Weeks Early
Weight Handicap (lb.)	2·26±0·65	0·98±1·24	2·44±0·56	3·20±0·76
Height Handicap (in.)	0·89±0·33	1·22±0·49	0·88±0·25	0·89±0·45

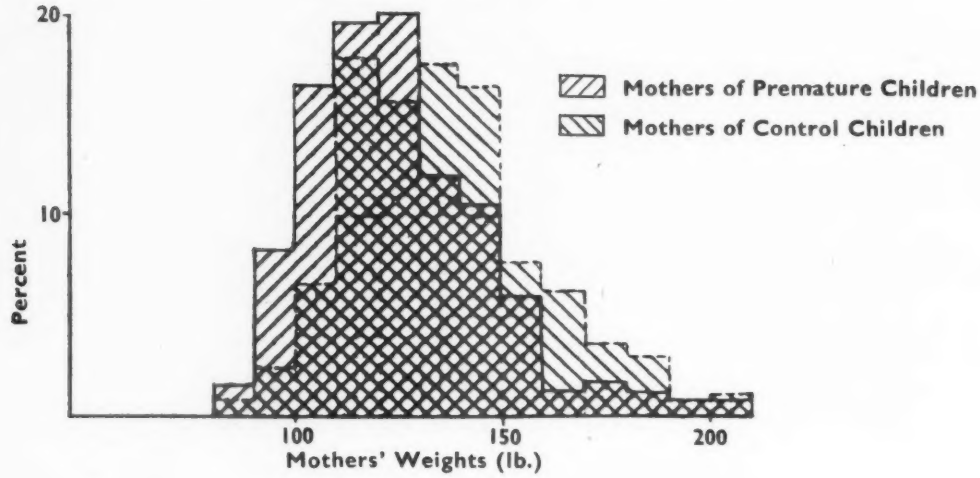
At 4 years of age the height handicap is similar in each group. The weight handicap, on the other hand, appears to be smaller among the children whose premature delivery was explained by toxaemia, ante-partum haemorrhage or induction; in particular it is small for the children in this group who were born more than four weeks early; there were only 49 of these children, however, and their weight handicap is not significantly lower than that of children in the other three groups; it appears low owing to the inclusion of three premature children, two of whom were 12 lb. heavier than their controls at 4 years and one of whom was 14 lb. heavier. The history of these children is interesting. One of them has spent more than half the first four years of his life in hospital where he was treated for bilateral cataracts; there is no obvious explanation for his abnormally large weight; his mother is only 8 lb. heavier than the mother of his control and the control himself is of average weight. The mothers of the other two premature children were respectively 69 lb. and 22 lb. heavier than the mothers of the matched controls, though their heights were similar. The former had had a surgical induction of premature labour, and the latter a premature delivery shortly after a fall.

Further examination of the figures in Table 7, taking into account the weight handicap at birth, does not yield any more meaningful results, and we can find no statistically satisfactory evidence that either the length of gestation or the history of the pregnancy is related to the 4-year-old physical handicaps of these children.

Handicaps of the Premature Child Related to his Mother's Height and Weight

It is well known that the heights and to a lesser extent the weights of children are related to the heights and weights of their parents, and it has been shown that the mothers of premature children are on the average smaller than the mothers of those weighing more than 5½ lb. at birth (Baird, 1945; Thomson, 1951). Accordingly it is of interest to see how far differences in the size of premature children and their controls are reflected in differences in the size of their parents. The measurements of both parents were asked for in this survey, but, since the fathers' heights and weights were recorded estimates and not actual measurements, we have thought it better to consider only the maternal measurements in the following paragraphs. The majority of the mothers were weighed and measured when they attended for the school clinical examination of their children in March, 1952. They were weighed when wearing indoor clothes.

Fig. 2 shows the frequency distributions of the weights and heights of the mothers of premature children compared with similar distributions for the mothers of the controls.



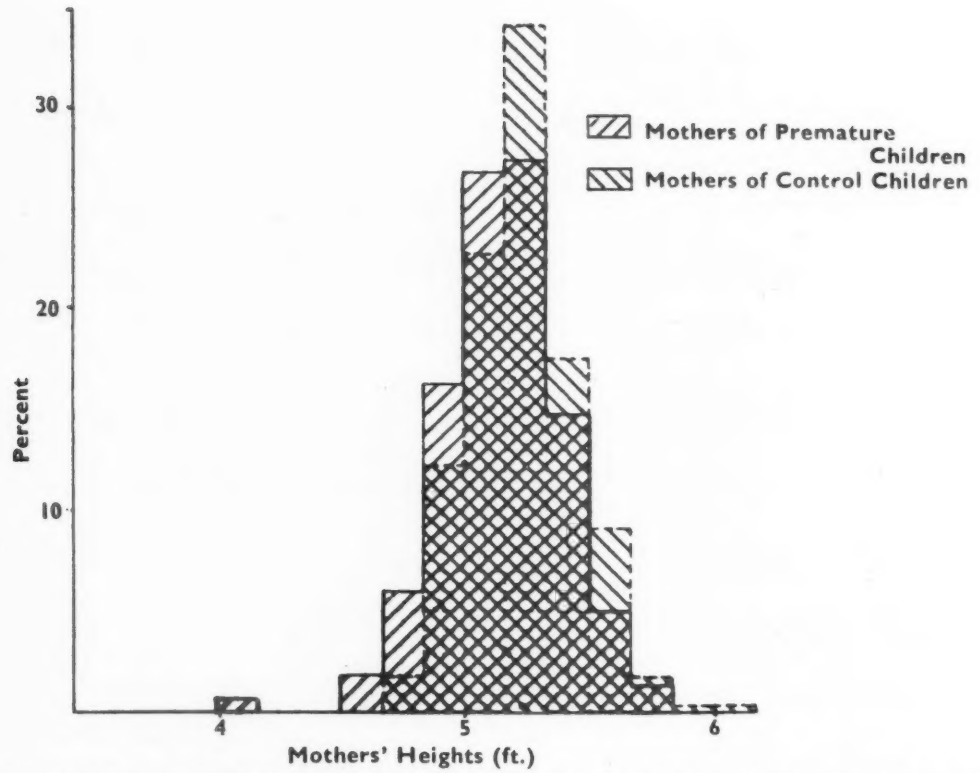


FIG. 2.—(*Above*) Percentage distribution of the weights of the mothers of premature children and of the mothers of their controls.
FIG. 2.—(*Below*) Percentage distribution of the weights of the mothers of premature children and of the mothers of their controls.

For each measurement the distributions are similar in shape for the two types of mother, but those for the mothers of premature children lie to the left of those for the mothers of the controls, that is to say they tend to be lighter and shorter.

Both the height of the mother and the height of her

child at 4 years are known for both members of 289 premature and control pairs. Among these the mothers of the premature children are $1 \cdot 05 \pm 0 \cdot 22$ in. smaller than the mothers of the controls, a figure that is closely similar to the difference in height between the children themselves, which for this group of 289 pairs is at 4 years $0 \cdot 89 \pm 0 \cdot 17$ in. There is a highly significant regression coefficient of $+0 \cdot 24$ ($t = 5 \cdot 57$ $n = 287$ $P < 0 \cdot 001$) relating the height differences between the pairs of children to the height differences between their mothers. By taking this factor into account, the variance of the height handicap of the premature children at four years is reduced by 11%.

Similarly, the weight of both mothers and children is known for both members of 283 pairs. The mothers of the premature children are $8 \cdot 94 \pm 1 \cdot 74$ lb. lighter than the mothers of the controls, whereas the average difference in weight between the children themselves is $2 \cdot 50 \pm 0 \cdot 37$ lb. There is a small regression coefficient of $+0 \cdot 027$ ($t = 2 \cdot 17$ $n = 281$ $0 \cdot 05 > P > 0 \cdot 02$) relating the weight differences of the children to the weight differences of their parents, but the effect of this factor on the variance of the weight handicap of premature children at 4 years is negligible.

We have next divided these mothers as follows: (*a*) Those belonging to the pairs in which the premature child had by 4 years caught up with or surpassed his control in weight, and (*b*) those belonging to the pairs in which the premature child was still lagging behind in weight at this age. The weight differences between the pairs of mothers in these two groups are shown in the first line of Table 8. The figures in the second line were obtained after regrouping the mothers into those whose children had eliminated their initial height handicaps, and those whose children were still lagging behind their controls in height at 4 years.

TABLE 8
WEIGHT AND HEIGHT DIFFERENCES BETWEEN MOTHERS OF CONTROLS AND MOTHERS OF PREMATURE CHILDREN

	(a) Premature Children who Have Caught Up	(b) Premature Children Still Handicapped in Height and Weight
Mothers' weight difference (lb.)	$+1 \cdot 92 \pm 2 \cdot 2$	$+12 \cdot 6 \pm 2 \cdot 6$
Mothers' height difference (in.)	$+0 \cdot 12 \pm 0 \cdot 34$	$+1 \cdot 82 \pm 0 \cdot 31$

The weight and height differences of the pairs of mothers in group (*a*) are not significantly different from zero and it appears that the mothers of the premature children who caught up, either in weight or in height, were drawn from the same weight or height populations as the mothers of the control pairs; on the other hand, the mothers of the premature children who did not catch up were drawn from a significantly lighter or shorter population.

As compared with the mothers of the controls, the women who suffered from abnormalities of pregnancy were on the average slightly taller and heavier than the women with no known cause for their premature delivery. Those with abnormal pregnancies were 7·0 lb. lighter and 0·84 in. shorter than the control mothers, whereas the corresponding figures for the mothers with normal pregnancies were 8·7 lb. and 1·4 in. Neither of these differences is significant.

It appears then that the height of a mother gives a better indication of the likely growth pattern of her premature baby than does the baby's weight at birth, the medical history of pregnancy, or the length of gestation, whether these three factors are considered separately or in combination.

Contribution of Premature Children to the Total Number of Stunted and Underweight Children in the Population

Though the average height and weight handicaps of premature children are small, it seemed possible that these average figures hid an excess of stunted and underweight children who, in the aggregate, might make a serious contribution to the physically handicapped children in the population. This suggestion receives no support from a comparison of the weight and height distributions of the premature children and their controls (see Fig. 1); but it has important implications and needs a more detailed study, which is given here.

We have taken as being stunted or underweight those children who at both 2 and 4 years were more than 1 standard deviation below the mean of the main survey population (see page 437) for either weight or height or both. The limiting measurements were 25 lb. or less and 31 in. or less at 2 years and 33 lb. or less and 38 in. or less at 4 years. The proportion of children separated out in this way is shown in Table 9 for three groups, premature children, their controls and the mature children of the main sample.

It will be seen that approximately three times as many of the premature children as of the controls were stunted or underweight at both ages. It is also of interest that the proportion of children of this type in the main survey sample is significantly smaller than in the control sample. This latter finding is presumably explained by the fact (Douglas and Mogford, 1953) that the controls, being matched with the premature children, were drawn from poorer homes than the rest of the mature children born during the survey week, and were more often female.

Although premature children yield more than their share of those that are stunted or underweight, they

TABLE 9

PERCENTAGE OF CHILDREN BELOW STANDARD FOR WEIGHT AND/OR HEIGHT AT BOTH 2 AND 4 YEARS OF AGE

Measurement(s) below Standard in Both Years	Premature Children (%)	Controls (%)	Main Sample (Children of Birth Weight over 5½ lb.) (%)	All Children (i.e. Main Sample Plus Premature Children) (%)
Weight only ..	15·4	6·8	5·0	5·4
Height only ..	6·2	1·8	1·4	1·6
Weight and height ..	8·4	2·3	1·7	2·0
Total % below standard ..	30·0	10·9	8·1	9·0
Number of children ..	356	385	8053*	8409

* When calculating the figures for the main survey sample, a correction has been made for the fact that, whereas all children in the upper social groups who were born in the first week of March, 1946, were enrolled in the survey, only one out of every four children in the manual working classes was enrolled (cf. Douglas, 1951). This correction is made by giving the former classes a weight of unity and the latter a weight of 4. It should be noted that *all* the premature children born during the survey week were followed up, whatever the social class of their parents.

contribute only a relatively small proportion of the children of this type in the whole population. Thus, out of a total of 758 children who were below the standard for height and/or weight, 107 (14·1%) were prematurely born. This percentage may be compared with the incidence of surviving premature children in the sample which is 4·2%. The 758 children below standard represent 9·0% of all the children born during the survey week and the removal of all prematurely born children from the sample would reduce this proportion by only 0·9%. Even this figure overstates the importance of prematurity *per se* for it does not allow for the fact that premature children come from the poorer homes and include an excess of females. If the mature children in the main sample had been selected in the same way as the controls, there would have been a total of 986 stunted or underweight children in the population of whom 10·9% (and not 14·1% as given above) would have been premature.

The smallest premature children (of birth weight 3½ lb. or less) are no more likely to be stunted or underweight than are the heavier ones. Thus, out of 13 of these children of low birth weight, three were underweight and one was both stunted and underweight: this is the number that would have been expected from the experience of the whole group of premature children.

We have examined the medical histories of all these stunted and underweight children. Of the five most physically handicapped three were mongols and one had spina bifida. Otherwise there was no evidence of an excess of chronically ill children among them or of a high incidence of abnormalities of pregnancy or gestation.

Comparisons Between Social Groups

Since the premature children in this inquiry have been compared with controls who were drawn from similar homes and had parents of the same social group, the observed deficiencies in growth are unlikely to be explained by the association of prematurity with poverty. But it is of some interest to see whether the premature children reared in relatively prosperous homes were better able to reduce their initial handicaps than were those reared in poorer homes. As judged by the mean differences between the pairs in both weight and height, the children of the more prosperous parents (non-manual workers) have by 4 years of age made a proportionately greater reduction in their handicaps than the children in other groups. The former have by 4 years of age reduced their initial weight handicap by 37% and their 2-year-old height handicap by 17% whereas the latter have shown a slight increase in both their weight and height handicaps. These differences, however, are not statistically significant and are not supported by a comparison of the incidence of stunted and underweight children in the two groups. Using the standards given in the preceding section, the ratio of stunted and/or underweight premature children to stunted and/or underweight controls was 3·5:1 in the non-manual working classes and 2·4:1 in the manual working classes. This difference again was not significant. There is no necessary conflict between these two findings which are at first sight contradictory. The proportion of premature children severely handicapped at 4 years might well be the same in all social groups, although on the average the premature child in a prosperous family has the greater chance of catching up. It is to be hoped that further information on this point will be forthcoming as we follow these children at later ages.

One further point of interest is that the mean difference in the heights of the mothers of the premature and control pairs is similar in each social group. For the non-manual workers it is $1 \cdot 04 \pm 0 \cdot 44$ in. and for the manual workers $1 \cdot 06 \pm 0 \cdot 26$ in.

CONCLUSIONS

Although, on the average, premature children do not reduce their initial weight handicaps during the first four years of their lives, or their two-year height handicaps between 2 and 4 years, there are considerable variations in the progress of individual children. It appears that the best guide to the growth of a premature baby is given by the height of his parents. Unfortunately we have only been able to

consider the heights of the mothers as it was impossible to arrange for the fathers to be measured. But maternal height alone was of greater value in predicting the subsequent growth of our premature children than were birth weight, length of gestation, the medical history of the pregnancy, or any combination of these three factors.

We do not wish to enter here into any detailed discussion of whether the shorter stature of the mothers of premature children arises from poor nutrition in early life or is genetically determined but the results of this inquiry suggest that the latter is the more probable explanation. We are doubtful about the importance of nutrition in this context because the mothers of our premature children were drawn from families that were closely similar in social and economic circumstances to those of the mothers of the controls. It may of course be objected that within the same social group the women with the poorest nutritional history (for example those coming from a poorer home than their husbands) are the most likely to have premature children and that our matching has not allowed for this. But this objection is hard to reconcile with the fact that the differences between mothers are just as large among the relatively well-to-do pairs as among those from the manual worker group. It is hoped that the study of prematurity now being carried out by the National Birthday Trust Fund will throw more light on this problem. Whatever the outcome, it is clear that assessments of the physical handicaps of premature children can have little meaning unless they are related to the size of their parents; this was to be expected and is only emphasized here because, to our knowledge, there has been no previous attempt to establish such a relationship.

SUMMARY

This paper describes the growth of a national sample of premature children who have been followed up from birth to 4 years and who, throughout this period, have been contrasted with a closely matched group of controls.

On the average the premature children have not reduced their weight handicap between birth and 4 years, and have not reduced their height handicap between 2 and 4 years.

By 4 years of age, 36% of premature children have caught up with or surpassed their controls in weight and 44% in height. There is a tendency for the smallest premature children at birth to be the most successful in eliminating their initial handicaps.

There is no statistically satisfactory evidence that premature children resulting from the shorter gestations or from complicated pregnancies differ in their rate of growth from the rest of the premature sample.

The mothers of premature children are on the average shorter and lighter than the mothers of the controls, and the premature children who are furthest behind their controls in weight or height tend also to be the ones whose mothers are furthest behind the mothers of the controls in these measurements.

The mothers of the premature children who, by 4 years have eliminated their initial weight or height handicaps, are as tall and as heavy as the mothers of the matched controls. In contrast the mothers of the children who are still lagging behind at this age are significantly smaller and lighter than the mothers of the controls.

Premature children yield more than their share of all children who are stunted or underweight. But removal of all premature children would make only a relatively small reduction in the numbers of children of this type in the whole population.

There is no satisfactory evidence that the premature children who come from the relatively well-to-do families are any more successful in reducing their physical handicaps than those from poorer families.

This follow-up survey of premature children is being made by a joint committee of the Institute of Child Health (University of London), the Society of Medical Officers of Health and the Population Investigation Committee. The chairman of the Committee is Professor James Young, the vice-chairman Professor A. A. Moncrieff and the secretary Professor D. V. Glass. The Nuffield Foundation has financed this inquiry during the pre-school years, and a grant for continuing it in the primary school period has been made by the Board of Governors of The Hospital for Sick Children, Great Ormond Street, through the Institute of Child Health.

We wish to thank the chairman and members of the joint committee for their help and advice; the medical officers of health and the health visitors whose generous cooperation made this survey possible; and the mothers in all parts of the country who willingly answered numerous and detailed questions on their children's health.

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THE EXCRETION OF SUGARS AFTER THE INTRAVENOUS ADMINISTRATION OF INVERT SUGAR

BY

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Until recently glucose was the only sugar used for intravenous administration. Glucose was indeed the obvious choice, for it is constantly present in the blood and it also occupies a central position in carbohydrate metabolism.

The results obtained by the intravenous administration of glucose are satisfactory. However, if glucose in a higher concentration than 5% is used difficulties may ensue. The wall of the blood vessel is affected by the hypertonic glucose solution, with the result that in many cases thrombi develop, and continued administration in the same vessel becomes impossible. Moreover, the intravenous administration of large quantities of 10% glucose causes glycosuria and results in increased diuresis. Not only is part of the glucose again lost in this way, but also the patient loses more fluid than was administered. In many cases in which fluid is administered intravenously this is undesirable. Other nutrients were therefore sought from which to prepare a liquid of high caloric value for intravenous administration.

As long as intravenous administration of fat is still in the experimental stage, only carbohydrates and amino-acids should be considered as sources of calories. The highest concentration of amino-acids which can be given intravenously in larger quantities is about 5%. If amino-acids are given fairly rapidly in higher concentration, nausea and vomiting will soon occur so that any increase in the caloric value of the infusion liquid must be by increasing the carbohydrate content. An infusion liquid containing 10% carbohydrate and 5% amino-acid has a nutrient value of 600 calories per litre. With such a liquid it is possible, provided the excretion of sugar and amino-acids in the urine is small, to meet to a great extent the caloric need of a patient. Weichselbaum, Elman and Lund (1950) suggested giving invert sugar instead of glucose. They observed that if 10% invert sugar and 10% glucose were administered at the same rate, the amount of carbohydrate in the urine after administration of glucose was about twice as great as after giving invert sugar.

Although fructose is less readily reabsorbed by the kidney than glucose, the rate of utilization of fructose in the body is so high that the fructose level of the blood remains low. The result is that excretion of fructose hardly takes place. This is due to the fact that fructose is absorbed more rapidly by the cells and phosphorylated than is the case with glucose (Cori, 1926). The phosphorylated product is then easily broken down by the organism into pyruvic acid, while at the same time glycogen may be formed (Soskin and Levine, 1952). There are signs which show that for carbohydrate metabolism liver tissue prefers fructose to glucose (Vestling, Mylroie, Irish and Grant, 1950). In some more recent reports the original observations by Elman are corroborated. It is a remarkable fact that the reaction of the vascular wall to 10% glucose is greater than to 10% invert sugar.

Lawton, Curreri and Gale (1951) on the other hand consider the advantages of invert sugar less important. The excretion during administration of 10% glucose is, according to them, not so great that the use of invert sugar is a marked caloric improvement. A secondary advantage is reduced diuresis after the administration of invert sugar.

The above-mentioned authors all carried out their observations on adults. However, the problem is also of importance in children, for it is desirable to have an infusion liquid available which will provide by intravenous alimentation not only sufficient fluid but also enough calories. Even more than in adults it is important in the growing child to maintain a caloric balance during acute disorders. For this reason we have studied the retention of intravenously administered invert sugar in children.

In connexion with the investigations by Elman we studied first the excretion of fluid and carbohydrates in a number of children who for 24 hours received either 10% glucose or 10% invert sugar. These children had been admitted to hospital for

TABLE 1

THE URINE OUTPUT AND CARBOHYDRATE EXCRETION AFTER INTRAVENOUS DRIP OF 10% GLUCOSE AND 10% INVERT SUGAR FOR 24 HOURS

Patient	Volume (ml.)	Carbohydrate (gr.)		Weight (kg.)		Urine Output (ml.)	Carbohydrate Excretion	
		Glucose	Fructose	Before	After		Glucose (gr.)	Fructose (gr.)
10% *Glucose*								
1	1,950	195	—	13·8	13·7	1,325	2·8	—
2	2,000	200	—	17·2	16·8	1,860	2·0	—
3	1,370	137	—	12·3	12·7	560	0·5	—
Mean	1,775	177·5	—	14·4	14·4	1,245	1·8	—
10% *Invert Sugar*								
1	1,200	60	60	10·6	11·5	770	0·7	1·3
2	2,000	100	100	16·5	17·5	1,300	3·4	1·0
3	2,000	100	100	17·2	17·2	1,200	2·6	0·6
Mean	1,735	87	87	14·8	15·4	1,090	3·3	1·0

some acute infectious disease, and, as they showed signs of shock, they were given an intravenous infusion. During the last 24 hours the infusion liquid was replaced by either 10% glucose or 10% invert sugar. In that period the urine was collected and the urinary glucose and fructose were determined by titration. The results are given in Table 1. None of the children who had been given 10% glucose by intravenous drip for 24 hours showed an appreciable excretion of glucose. Only 1·4%, 1·0% and 0·4% of the administered glucose was eliminated.

For the patients who had been given invert sugar the percentages for total sugar excretion were: 1·7%, 2·2% and 1·6%. The sugar excreted by these patients was partly glucose and partly fructose. The glucose excretion amounted to 0·6%, 1·7% and 1·3% respectively of the total quantity of administered sugar. The fructose excretion was small, only 1·1%, 0·5% and 0·3% of the total quantity of administered carbohydrates.

The total sugar excretion of the children who were given 10% glucose was even lower than in the other group. Calorically, however, the loss in both groups is insignificant. In this respect and under these conditions invert sugar does not produce an improvement.

It is remarkable that although both groups eliminated an almost equal amount of sugar the output of urine differed. After administration of glucose the urine output averaged 1,245 ml. After administration of invert sugar this figure was 1,090 ml. The body weight of the children before and after infusion was in agreement with these figures. In the group given invert sugar there was an average increase of 0·6 kg.

In order to obtain a better insight into the differences in excretion during intravenous administration of glucose and fructose, we gave for a short time a larger quantity of 10% glucose and 10% invert sugar to some of the children (Table 2).

Table 2 shows that the urinary glucose output at this rate of infusion for the 10% glucose solution has become considerable, averaging 17·8% of the administered amount. For the 5% glucose solution the loss amounts to 6·4% of the quantity given.

TABLE 2

URINE OUTPUT AND CARBOHYDRATE EXCRETION AFTER INTRAVENOUS ADMINISTRATION OF 5% AND 10% GLUCOSE AND 10% INVERT SUGAR

Patient	Time (min.)	Weight (kg.)	Volume (ml.)	Urine Output (ml./9 hr.)	Carbohydrate (g.)	Carbohydrate Excretion (g./9 hr.)	
						Glucose	Fructose
5% *Glucose*							
1	60	21·6	1,000	1,002	50	2·0	—
2	60	22	1,000	926	50	6·0	—
3	110	43·7	1,000	1,448	50	2·2	—
4	60	20·7	1,000	765	50	2·5	—
Mean	72·5	27	1,000	1,037	50	3·2	—
10% *Glucose*							
1	60	28·4	1,000	1,080	100	15·9	—
2	80	43·6	1,000	1,008	100	13·1	—
3	90	24	1,000	1,183	100	15·8	—
4	60	21·2	1,000	1,230	100	26·4	—
Mean	72·5	29·3	1,000	1,125	100	17·8	—
10% *Invert Sugar*							
1	60	30·6	1,000	960	100	12·0	1·00
2	60	30·3	1,000	740	100	7·5	1·00
3	60	31	1,000	418	100	3·0	0·40
4	90	45·7	1,000	953	100	2·4	0·60
Mean	67·5	34·4	1,000	768	100	6·25	0·75

The losses of invert sugar are 12·5% of the glucose given and 1·5% of the fructose. This shows that the loss of fructose is very small. It is remarkable that fructose increases the loss of glucose. Whereas during administration of 5% glucose the loss amounted to 6·4%, this rose after the addition of 5% fructose to 12·5%, double the amount.

utilization of fructose the tissues have less need of glucose, so that the glucose in the blood rises to a higher level than is the case during administration of 5% glucose only.

Also remarkable is the small output of urine after the administration of invert sugar, viz. 768 ml. as against 1,127 ml. after the administration of 10% glucose.

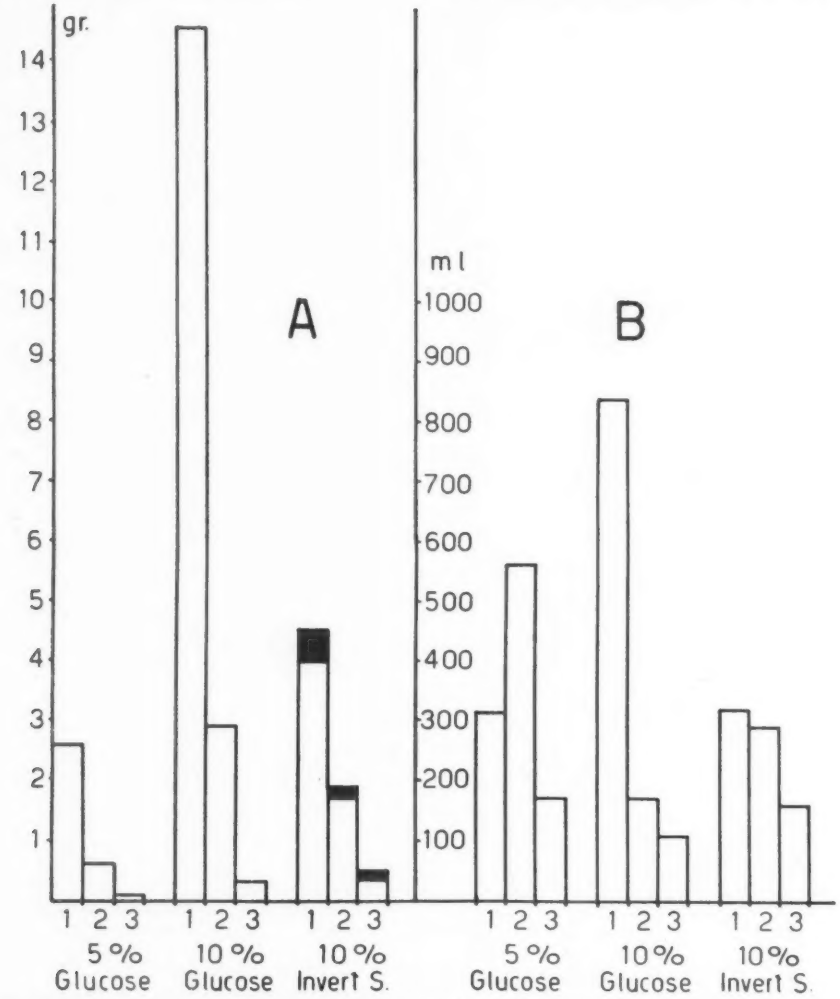

FIG. 1.—The relation between urine output, carbohydrate excretion and time. *A* shows carbohydrate excretion: (1) during infusion (average duration approximately 70 min.); (2) in the first three hours after the end of the infusion; (3) from the fourth to tenth hour after the end of infusion. *B* shows the urine output under the same conditions. □ glucose output. ■ fructose output.

Nevertheless, the total loss remains considerably smaller than after the administration of 10% glucose; in that case the loss is 17·8 g. as against a total of 7 g. after the administration of invert sugar.

It is possible that fructose renders the reabsorption of glucose in the kidneys less complete. However, this is not likely, considering the low blood level which is in agreement with the urinary fructose output found. It is more likely that owing to

Apparently fructose in some way or other retains fluid. This shows that the metabolism of fructose is not altogether similar to that of glucose. Since patients who need intravenous alimentation generally suffer from dehydration, this tendency of invert sugar to reduce diuresis is of practical importance. How this fluid retention is brought about is not certain.

In view of the low fructose level in the blood found

after intravenous administration, it is unlikely that the quantity of extracellular fluid has increased.

In this connexion there is a striking difference in the time in which the largest quantity of urine is produced. Fig. 1B shows that in the case of the 5% glucose solution the largest of urine output is after all the fluid has been administered. For the 10% glucose solution this appears not to be so, while for a 10% invert sugar solution the urine output is at first the same as that after the use of 5% glucose but in the period after intravenous administration it is markedly smaller. This finding is the more remarkable as such differences are not found in the excretion of carbohydrates (Fig. 1A).

Discussion

Albanese, Felch, Higgons, Vestal and Stephanson (1952) demonstrated that fructose more than glucose stimulates the protein synthesis in the growing baby. Fructose might be called the sugar of the young foetus during intra-uterine life. The seminal vesicle as well as the endometrium contains fructose (Mann, 1949). The placenta is capable of converting glucose into fructose.

In many animal species the blood sugar of the foetus is largely fructose (Huggett, 1952). In these animals the amniotic fluid contains fructose (Okamura, 1938). In women fructose has disappeared from the blood in the second half of pregnancy. The placenta in women, however, also contains an enzyme capable of converting glucose into fructose. Administration of fructose to young children is therefore indicated in view of their embryonic development. By stimulating protein synthesis fructose will at the same time promote water retention. During a short period of administration such as we have adopted it is unlikely that the cause of fluid retention will be found in accelerated protein anabolism. It seems more plausible that an accumulation of intermediate products from sugar metabolism has a water-retaining effect.

In view of the tendency to reduce diuresis and the rapid utilization of fructose by the cell, invert sugar is more suitable for intravenous administration than glucose of the same concentration, particularly if the concentration exceeds 5%.

The smaller loss of sugar during administration of invert sugar described by Elman *et al.* is important only if large quantities are given in a relatively short period of time.

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SOME OBSERVATIONS ON UMBILICAL HERNIA IN INFANTS

BY

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The common condition of infantile umbilical hernia may cause considerable concern among mothers, and there still seems to be some diversity of opinion concerning appropriate treatment. It is probable that the condition is present in one baby in six.

In this paper I have considered 283 infants with umbilical hernia. The time of the first appearance of the hernia has been noted and particular attention has been given to the study of treatment and general prognosis.

Historical

The condition of the umbilical cord at birth and the umbilicus during infancy has aroused the interest of medical authors down the centuries. Celsus (1st century A.D.) describes an operation by 'ligature' for umbilical hernia at 7 to 14 years. Soranus (A.D. 98-117) suggests that 'it is better to double the cord over and roll it in a little bit of wool and then lay it gently against the middle of the navel, for perchance by the pressure of its weight the part will be moulded to a better shaped depression'.

Widal de Cassis (1848) first described the umbilical fascia as immediately superficial to the parietal peritoneum and posterior to the linea alba and derived from the transversalis fascia.

Richet (1856) considered the fibrous make-up of the umbilical ring and demonstrated that the umbilical ring cannot be closed by direct muscular action but in early infancy it is reinforced by elastic fibres from the obliterated umbilical arteries and takes on the nature of a sphincter. Richet also described an umbilical canal, and he postulates three main types of umbilical hernia—the congenital, the infantile and the adult hernia.

Levadoux (1907) (as quoted at length by Allen) noted the variations in the umbilical fascia and in its disposition, and of the remnants of the umbilical arteries and veins and of the urachus. He concluded that the local fibrous tissue does not reach its full development until after puberty.

More recently Gorelow (1934), on the evidence of 300 dissections, agrees with Richet concerning the identity of an umbilical fascia and umbilical canal.

No case of strangulation of an infantile umbilical hernia has been recorded, and Erichsen (1884) declares that 'these small umbilical herniae are never strangulated and consequently never cause death, yet it is very rare to see one in a child of ten years of age, though in infants we meet them by the score'. Nearly all writers have advocated strapping or a truss or some other restrictive appliance. Opinion on operation has varied if the hernia has not made a spontaneous cure by three to six months of age (Herzfeld, 1938) or to wait as late as five to seven years (Fèvre and Barcat, 1947).

Embryology

Wyburn (1939) has shown that the mature umbilical cord contains vestiges of the allantois, the omphalomesenteric duct (yolk sac) and the extra-embryonic coelom, and is mainly composed of connective tissue formed from the primitive mesoderm. The abdominal parietes, i.e., the rectus sheath, the linea alba and the fascia of the anterior abdominal wall, are formed from intra-embryonic mesoderm which has its origin as the middle layer of cells in the embryonic plate. Fusion of these two distinct forms of mesoderm is at the embryonic rim which is the future umbilical orifice. Proliferation of lateral connective tissue plates passes from the umbilical cord at this point and is responsible for closure of the umbilical ring. A failure in the normal growth of the dense connective tissue which should ultimately occupy the umbilical ring may contribute to local congenital abnormality. In the greater dis-

order, exomphalos, the supra- and infra-umbilical portions of the abdominal wall have formed, but the intervening area is covered only by amnion and there is no proper umbilical ring.

'Herniae into the umbilical cord' may be considered to be the contrary type of failure. At birth it is evident that a portion of gut has failed, during embryonic life, to return normally into the abdominal cavity through a narrowed neck. The intestinal wall is usually firmly adherent to the upper rim of the umbilical orifice and the 'hernia' cannot be automatically reduced into the peritoneal cavity.

The commonest type of abnormality is when the umbilical ring does not close. A true hernia presents through the ring within a peritoneal sac. The ultimate closure of the umbilical ring depends upon the proliferation of encircling mesoderm. When this obliterative proliferation is incomplete a patent umbilical ring is the result and herniae through this ring during infancy are under particular consideration in this paper.

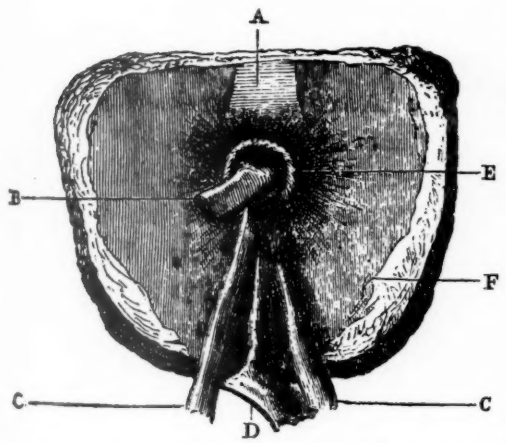
Anatomy

From anatomical descriptions and evidence obtained by dissections on 20 neonates it is possible to give a simple picture of the anatomy. The umbilical region is bounded laterally by the rectus muscles enclosed in their sheaths, posteriorly by the parietal peritoneum and anteriorly by the skin. At the umbilical orifice in the linea alba the fibrous remnants of the umbilical arteries are firmly attached to the lower edge of the orifice. The venous remnants are loosely attached to the superior edge of the orifice but are more firmly attached to the inferior and lateral edges (Fig. 1*a*). This was noted by Richet (1856). A large amount of embryonic connective tissue fills the lower portion of the umbilicus with a firm layer of tissue which helps to act as an efficient barrier against the development of a hernia (Moschcowitz, 1915).

Dissections have been made on stillborn infants whose umbilical cord was still present. Wharton's jelly was first dissected away. The still patent arteries and vein then lay loose in the dissection and their course through the umbilical orifice to their destinations could be traced. It was then found that the arteries were firmly attached to the lower edge of the umbilical orifice and the corresponding region of the anterior abdominal wall. The umbilical vein had no such attachment and could easily be pulled in and out of the orifice. Whether or not the obliterated vein later became attached to the inferior edge of the umbilical orifice could not be verified by dissection. Thus it is suggested that the umbilicus is weakest at the upper edge of the orifice. Usually hernia presents at the upper edge of the umbilicus.

The umbilical orifice is thus essentially a gap in the linea alba. The size of the gap varies considerably and the recti play no part in its direct formation. By dissection it was found that at the level of the umbilicus the edges of the two recti were separated by 1 to 1·7 cm. The recti in infants are more divaricant supra-umbilically than infra-umbilically and 1 to 2 cm. below the orifice the recti muscles are in close apposition at all ages and the linea alba is only a fibrous raphe. This factor, coupled with the additional strength of the inferior edge of the umbilical orifice, creates an effective anatomical barrier against infra-umbilical herniation.

Some divarication of the recti is common in infants and it is possible for wide divarication to be present without a hernia. Alternatively, widely divaricant recti are compatible with a spontaneous disappearance of an umbilical hernia. The tonicity of these muscles is however, of considerable importance. The rectus muscles are attached to the posterior surface of their sheaths and thus to the linea alba by fibrous insertions. Many anatomical studies show that one set of these insertions is always at the level of the umbilicus. Hamilton has noted that 'tendinous fibres develop in fascia in direct response to mechanical stress'. Thus the tone and strength of the rectus muscles undoubtedly affect the strength of the linea alba and the fascial covering of the anterior abdominal wall.



Cette figure représente la face postérieure de l'anneau ombilical chez un enfant 48 heures après la naissance.

A. La ligne blanche.

B. La veine ombilicale.

C, C. Les artères ombilicales.

D. L'ouraque.

E. L'anneau élastique ou sphincter ombilical.

F. Le péritoine décollé.

FIG. 1*a*.—Richet's original drawing (*Arch. gen. Méd.*, 1857, **1**, 62) showing the loose attachment of the umbilical vein to the walls of the orifice and the much firmer attachment of the arteries and urachus.

The umbilical fascia is a direct extension of the transversalis fascia. Gorelow (1934) observed that it was represented by a small number of obliquely running fibres, varying from 0·5 cm. to 6·5 cm. in height. It varied in strength and in position, sometimes lying entirely above the umbilical orifice, sometimes over the orifice, only rarely below the orifice, and always firmly adherent to the peritoneum.

My dissections have confirmed that at the level of the orifice the peritoneum becomes thickened and somewhat toughened and appears to be reinforced by fibrous tissue. Richet considered that this fascia develops in strength during the early months and strengthening the superior edge of the umbilical orifice forms a protection against hernia.

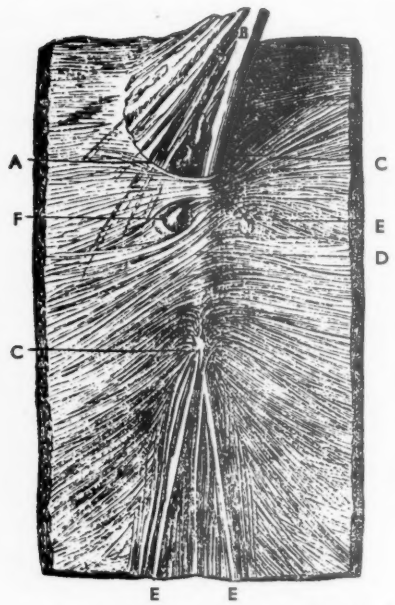
Where there is no appreciable umbilical fascia the peritoneum is not supported and a direct umbilical hernia may form through the umbilical orifice. It is probably this type of hernia which occurs in infants, particularly in premature infants, and spontaneously disappears in the first few months.

Various workers have postulated the existence of an umbilical canal, formed anteriorly by the linea alba, posteriorly by the umbilical fascia and laterally by the medial edges of the rectus sheaths with an entrance up to 3·6 cm. above the site of the obliterated umbilical veins, while in the canal the vein is loosely surrounded by adipose tissue. Richet's original drawings are shown in Figs. 1*b* and 1*c*.

The umbilical canal, like the inguinal canal, traverses obliquely the abdominal parietes from the peritoneum to the skin surfaces and both have a similar posterior surface of transversalis fascia and peritoneum. It is suggested that herniation down this canal leads to the adult type of umbilical hernia.

It appears that there are two main types of umbilical hernia. A direct umbilical hernia can form through the umbilical orifice when there is an absence or weakness of fascial strengthening. The hernia tends to 'point' at the superior edge of the umbilical orifice as this area is less strengthened by fibrous tissue. This may be the common type of umbilical hernia seen in infants. It is not affected by the presence or absence of divarication of the recti. The hernia tends to be cured spontaneously when the fascia of the abdominal wall has increased in strength. A fairly wide umbilical orifice does not necessarily mean the presence of a hernia, and a hernia may disappear before the orifice has completely closed.

An oblique umbilical hernia may take place through the umbilical canal in later infancy, childhood or adult life. A portion of omentum or bowel passes down the umbilical canal and presents at the



A. L'ouraque et les artères ombilicales soudées à la cicatrice ombilicale

B. La veine ombilicale.

C, C. Ouverture par laquelle la veine ombilicale pénètre dans la gouttière ou canal ombilical.

D. Fascia ombilicalis, dont les fibres ferment en arrière la gouttière ombilicale.

E, F. Hernies graisseuses s'échappant à travers des éraillures du fascia ombilicalis.

FIG. 1*b*.—Richet's original drawing (*Arch. gén. Méd.*, 1856, 2, 648) showing the posterior surface of the anterior abdominal wall after the peritoneum has been removed revealing the umbilical canal.

A. Cicatrice ombilicale ou fusion de l'ouraque, des artères et de la veine ombilicales.
B. La veine ombilicale.
C. Terminaison de la gouttière ombilicale, au fond de laquelle se voit l'espace circonscrit par la demi-circonférence superieure de l'anneau et la cicatrice.
D, D. Artères ombilicales.
E, E. La gouttière ombilicale; la graisse a été enlevée, la veine isolée, et les fibres aponévrotiques qui ferment le fond de la gouttiére disséquées.
F, F, F, F. Débris de l'insertion du fascia ombilicalis.
G, G, G. Vaisseaux pénétrant à travers les faisceaux fibreux.
H. H. Les faisceaux fibreux qui forment paroi antérieure de la gouttière.

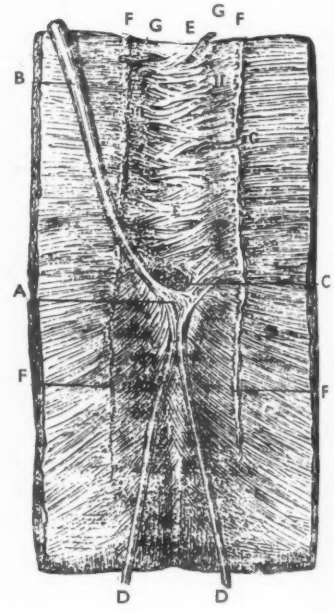


FIG. 1*c*.—Richet's original drawing (*Arch. gén. Méd.*, 1856, 1, 650) showing a similar dissection after the removal of the umbilical fascia.

upper edge of the umbilicus. This type is more likely to be persistent and surgical complications might occur.

No essential advances in these aspects of the anatomy of umbilical herniation have been made since Richet's (1856) original publication. His observations on the different anatomical arrangement of infantile and adult hernia closely approximate to the present clinical findings.

Umbilical Hernia in Infancy

Celsus defines a true hernia as a 'protrusion of loop or knuckle of an organ or tissue through an abnormal opening'. I have accepted as the criterion of diagnosis the presence of a saccular swelling which protrudes on coughing or crying and which can be reduced by simple pressure through a gap in the umbilicus. By contrast, the absence of any saccular protrusion despite the palpability of a gap at the umbilical orifice would indicate the absence of a true hernia. It should be noted that in some infants at birth there is an unusual length of skin on the umbilical cord which when the cord separates may falsely suggest a hernia (Fig. 2).

My clinical study of umbilical hernia comprises 283 infants in whom the hernia appeared before the age of 2½ years. Clinical details of the birth, the birth weight, the length of the cord, the day of separation of the cord, the time of appearance of the hernia and the possible related causes have been obtained. Of these infants, 140 were seen at an infant welfare clinic and the remaining 143 were observed in a hospital surgical out-patient department.

Infants who first attended under the age of 3 months at the same infant welfare clinic were taken as controls. With the assistance of health visitors a complete follow-up has been possible, and no control infants have shown any tendency to umbilical hernia.

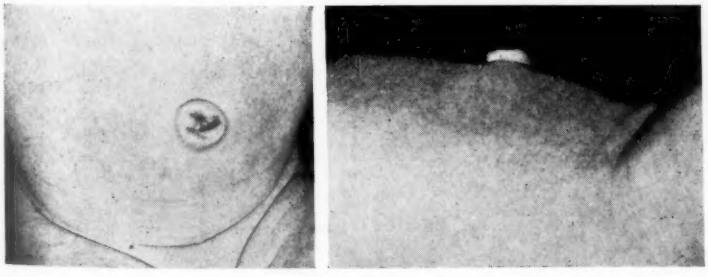


FIG. 2.—Baby aged 3½ weeks (10 lb. 12 oz. birth weight). The umbilical protrusion is due to an excessive amount of skin only. No umbilical orifice was palpable. The umbilicus was still moist. Strapping was not indicated and would have aggravated the septic condition of the umbilicus.

Frequency

Out of a total of 573 infants who were brought to the infant welfare clinic between December, 1948, and July, 1951, 106 developed an umbilical hernia before the age of 6 months. This is an incidence of 1 in 5·4.

Type of Birth

Table 1 compares the type of birth in 276 infants with umbilical hernia with 453 controls who were born between December, 1948, and July, 1951, in the same area as the clinic cases, on the basis of information obtainable from hospital and midwife records.

TABLE 1

COMPARISON OF TYPE OF BIRTH IN AFFECTED INFANTS AND CONTROLS

Type of Birth	Umbilical Herniae		Controls	
	No.	% of Total	No.	% of Total
Normal birth ..	244	88·9	439	96·9
Forceps	5	1·9	8	1·7
Breech	7	2·5	3	0·7
Caesarean	5	1·9	3	0·7
Twins	13	4·8	0	0·0
	274	100	453	100

These figures show significantly that hernia occurs more frequently in twin births. In fact, all the twins seen in the survey developed umbilical herniae. There is a possible tendency for a higher incidence in breech births.

The birth weights of infants developing umbilical hernia and of controls are shown in Table 2 and Fig. 3.

It will be noted that 2·8% of the controls were under 5½ lb. at birth. 9·0% of the affected children were under 5½ lb. at birth, 5·3% of the controls were over 9 lb. at birth and 9·0% of the affected children were over 9 lb. at birth. There is, therefore, evidence that umbilical hernia is more common in premature babies (i.e., 5½ lb. or less at birth) and a suggestion that the same is true of babies above 9 lb. at birth. The incidence in large babies may be due to a larger cord, which may be particularly noticeable in some large babies.

Length of Cord

The length of the cord at birth was

TABLE 2

BIRTH WEIGHTS IN AFFECTED INFANTS AND CONTROLS

Birth Weight (lb.)	Herniae		Controls in Same Area	
	No.	%	No.	%
Under 3	0	0·0	0	0·0
3-3½	0	0·0	2	0·4
3½-4	0	0·0	1	0·2
4-4½	4	1·5	0	0·0
4½-5	6	2·2	2	0·4
5-5½	11	4·1	8	1·7
5½-6	24	9·0	22	4·7
6-6½	16	6·0	51	10·9
6½-7	40	14·8	62	13·2
7-7½	51	19·0	77	16·4
7½-8	49	18·3	86	18·3
8-8½	29	10·7	90	19·1
8½-9	15	5·6	44	9·4
9-9½	8	3·0	12	2·6
9½-10	7	2·5	8	1·7
10-10½	7	2·5	3	0·6
10½-11	0	0·0	1	0·2
11-11½	1	0·4	1	0·2
11½-12	0	0·0	0	0·0
12-12½	1	0·4	0	0·0
	268	100	470	100

obtained wherever possible and compared with the controls (Table 3).

I am indebted to Dr. G. Herdan for the following comment on these figures:

TABLE 3

Length of Cord in Affected Infants (in.)	Controls
0-6 (0)	
6-12 (1)	
12-18 (7)	20
18-24 (20)	36
24-30 (12)	6
Over 30 (0)	2
40	64

> 'Although numbers in Table 3 are not sufficient for statistical testing of any difference that may exist in the two distributions, yet mere inspection shows distributions so strikingly different that the influence of the length of the cord upon the investigated phenomenon seems at least likely.'

I have no evidence to explain a possible relationship between length of the cord and the occurrence of umbilical hernia, nor have I evidence that traction on the cord during birth contributes to a hernia, although a possibility is suggested by the somewhat higher incidence in breech births.

Day of Separation of Cord

TABLE 4

DAY OF SEPARATION OF THE CORD

Day	Affected Children	Controls
3rd	1 (0·7%)	
4th	4 (3·0%)	12 (5·0%)
5th	20 (14·9%)	30 (12·5%)
6th	37 (27·6%)	74 (30·7%)
7th	26 (19·5%)	53 (22·0%)
8th	23 (17·2%)	32 (13·3%)
9th	9 (6·7%)	24 (10·0%)
10th	9 (6·7%)	9 (3·7%)
11th	2 (1·5%)	3 (1·2%)
12th	1 (0·7%)	3 (1·2%)
13th		1 (0·4%)
14th	2 (1·5%)	
15th		
	134 (100%)	241 (100%)

No significant difference is noted between the hernia cases and the controls and no evidence is obtained that the type of treatment of the cord after birth has an influence on the later development of a hernia.

Of the various modes of dressing the cord, it was noted that of 43 infants treated by a method in which no dressing or binder is applied but the cord is merely covered with collodion and allowed to drop off, 10 developed herniae, a similar incidence to that in the more orthodox method of treating the cord.

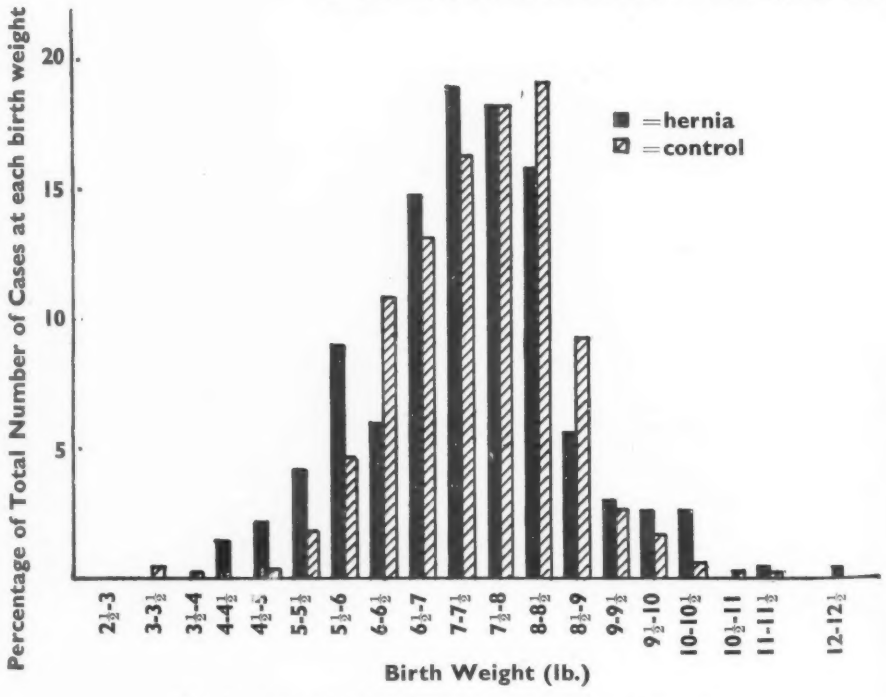


FIG 3.—Percentage of total number of cases at each birth weight.

Condition of Umbilicus after Separation of Cord

A common belief is that sepsis of the umbilicus after separation of the cord tends to induce a hernia. The condition of the umbilicus after separation of the cord was carefully recorded in all children who later attended the infant welfare clinic both in those who ultimately developed hernia and in the controls. In the majority of cases the umbilicus became dry within a few days of separation of the cord and no further dressing was required. In some cases minor local bleeding recurred for several weeks. In others the umbilical area became frankly septic with a purulent discharge, the folds of skin around the umbilicus becoming crusted and adherent with pus. In a small number of cases this septic condition led to the formation of a local soft granuloma, which could readily be distinguished from a cord stump which was firm and tough.

Table 5 gives the incidence of five common conditions in the affected children and in the controls.

TABLE 5

INCIDENCE OF COMMON CONDITIONS IN THE AFFECTED CHILDREN AND CONTROLS

Condition of Umbilicus	Affected Children	Controls
Healthy	184 (76·3%)	364 (77·9%)
Bleeding	15 (6·2%)	25 (5·4%)
Mild sepsis	37 (15·4%)	46 (9·9%)
Granuloma	0 (0·0%)	30 (6·4%)
Stumps	5 (2·1%)	2 (0·4%)
	241 (100%)	467 (100%)

These figures suggest a greater tendency for a hernia to develop after mild sepsis. A significant fact is that no case of umbilical hernia occurred after granulation. A direct follow-up of a further 28 cases of umbilical granulation personally treated has revealed no example of herniation. It is presumed that the umbilical orifice becomes firmly closed by scar tissue.

Size of the Umbilical Orifice

Routinely at the baby's first attendance at the clinic the size of the gap in the linea alba at the umbilicus was recorded. It was noted in many cases that the orifice through which the umbilical arteries and veins had passed into the cord appeared to be closed. One was, therefore, tempted to believe that a hernia would not develop. Sometimes there was a large gap, but such a gap did not always indicate a future hernia. It is interesting to note that in five neonates with a particularly large gap, sufficient to engage the little finger, no hernia subsequently developed, even though one infant had an attack of whooping cough. The possible anatomical explanation for this has been noted (vide supra). The incidence of gaps was recorded in the last 310 seen at the infant welfare clinic. (1) Quite a definite gap without a hernia was noted in 19 cases. None of these cases developed a hernia within the first six months of life. (2) A very slight pinpoint gap was noted in 50 cases, but none developed hernia. (3) The orifice appeared closed and there was no sign of an orifice to the examining finger in 167 cases and none of these developed hernia. (4) The orifice appeared closed as in (3) and yet a hernia developed later in seven cases. (5) A gap and a hernia were noted in 54 cases. (6) A granulation which required treatment was noted in 13 cases and thus a gap could not be palpated. (7) In three there was no gap but marked divarication of recti was noted. It is probable, therefore, that the palpable size of a gap in the linea alba at the umbilicus in early infancy is not an essential and determining factor as to whether a hernia will develop or not.

Family History

In 264 cases where a family history could be obtained 32 gave a definite history of a hernia in a brother, sister or parent. But many may have forgotten about a small hernia in another child. It is a common observation at the clinic that if one infant has a marked hernia frequently the next baby in the family has one also.

Associated Inguinal Hernia

Of these 283 cases, nine children had an inguinal hernia in addition to an umbilical hernia. Although it is known that both inguinal herniae and umbilical herniae have a higher incidence in premature babies only three of these nine cases were, in fact, premature babies. Two other cases of a umbilical hernia had the allied condition of hydrocoele of the hernial sac. Thus it was noted that 11 cases of inguinal hernia, all requiring operation, occurred in 283 cases of umbilical hernia, whereas in 213 controls in the year December, 1948, to December, 1949, there were only two cases of inguinal hernia.

Associated Supra-Umbilical Herniae

As suggested above, when firm fascial coverings of the abdominal wall at birth are not formed, both a weakness of the umbilical orifice and a weakness in the linea alba may result. A small supra-umbilical hernia may therefore co-exist with an umbilical hernia, and this was noted on seven occasions. In one of these cases the gap through which the umbilical hernia protruded was an indefinite oblong shape, possibly emphasizing the existence of weak fibrous tissue. It is possible for a supra-umbilical hernia to occur in the absence of true umbilical hernia and

this was so of the only case mentioned in the birth records. These supra-umbilical herniae tend to be cured spontaneously in a similar manner to an umbilical hernia, presumably due to the development of the umbilical fascia in later infancy.

Umbilical Hernia in Coloured Children

There is a widespread opinion that umbilical hernia is an almost universal condition in coloured children. I have been interested to note, for example, that English fathers who have served abroad have remarked on the size of umbilical hernia in native children and in consequence have been unable to understand their wife's concern over the comparatively small size of the hernia in their own babies. The condition in coloured babies has been ascribed to malaria or other diseases causing a large liver or spleen. There have been four full negro babies at my infant welfare clinic in the last two years. One had a severe umbilical granulation and no hernia developed. The other three children developed hernia. Two cleared up in a few months but the other, which was the largest hernia seen in this series, ultimately reached operation (Fig. 4). These four were healthy babies born in England, and had no evidence of malaria.

Cullen (1916) considered the higher incidence among coloured babies to be due to a thicker cord and a larger umbilicus. Mori (1938) observed a seasonal occurrence of hernia corresponding approximately to the curve for craniotabes and rickets, i.e., the incidence being highest among babies born in January. This finding may, I think, have some relationship to respiratory infection. Jones (1941) was unconvinced that the high incidence of umbilical hernia in negro babies was related either to malnutrition, rickets or a large cord. Information received from Nigeria indicates that umbilical hernia is very common among babies there, but they nearly always disappear spontaneously and a senior medical officer states that he has never heard of a case of hernial strangulation. Probably the higher incidence in coloured babies represents an inherited trait.

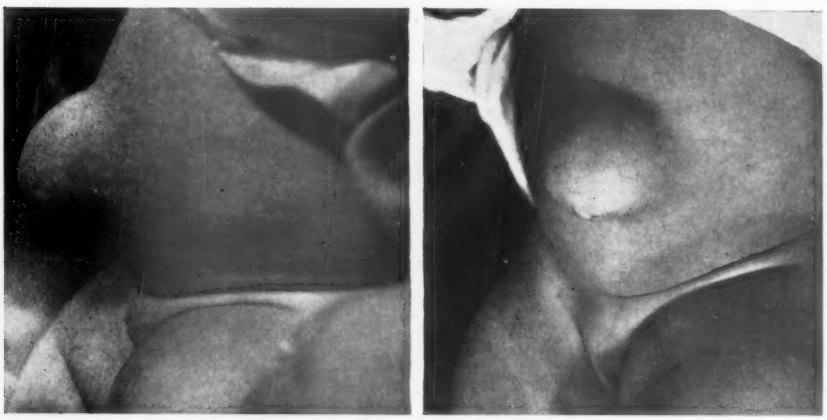


FIG. 4.—A negro baby aged 14 months was first seen when the umbilical orifice was 3 mm. in size and there was little umbilical protrusion. After five months' continuous strapping the size of the umbilical orifice was 12 mm. The umbilical area was continuously strapped until the condition was as shown above, she had no symptoms.

Immediate Causes for the Development of Umbilical Hernia

The preceding observations give a picture of the possible inherent natal and post-natal factors that may influence the later development of an umbilical hernia. However, in many cases there appeared to be an immediate physical cause for the occurrence of the hernia, such as coughing, crying or vomiting.

Mothers frequently stated that the hernia was noted directly after the child's birth (Table 6). This appeared to be erroneous information, since in only one case was an umbilical hernia mentioned in the birth records and that particular hernia was, in fact, supra-umbilical. It would, therefore, be more accurate to regard these hernias as developing in the early weeks of life, possibly soon after the separation of the cord. The initial appearance of an infantile umbilical hernia after the age of 6 months is comparatively rare. Only one case was noted as late as 2½ years of age. Fig. 5 shows the time of the first appearance of the hernia in the out-patient and cases seen at the infant welfare clinic. The latter were seen personally and may be more accurate.

Though a hernia may develop in a healthy, full-term, breast-fed baby, some immediate cause for the hernia was often apparent, as Table 7 shows.

Crying. Crying is often blamed by the mother as the cause of the hernia. In one case the parent gave a definite day and hour, and stated that the child cried all day and the hernia made its first appearance in the evening. Nine hospital cases appeared to be of this type and five of these had an associated inguinal hernia.

Coughing. In 16 hospital cases the hernia was reputed to have occurred during one particular attack of bronchial trouble. In a few of the clinic cases where the mother blamed a cough, a definite orifice had previously been felt in the linea alba, and it was considered

TABLE 6
AGE OF FIRST APPEARANCE OF HERNIA

Age (Months	No. of Hospital Cases*	No. of Clinic Cases†
0-1	54	13
1-2	37	72
2-3	6	29
3-4	7	10
4-5	2	1
5-6		
6-7	5	
7-8	2	3
8-9	1	
9-12	9	
12-15	2	1
15-18	1	
18-21	5	
21-24	2	
24-	1	

* According to mother's history. † Personally seen.

TABLE 7
IMMEDIATE CAUSE FOR DEVELOPMENT OF HERNIA

Cause	No. of Out-Patient Cases	No. of Infant Welfare Clinic Cases
Persistent crying ..	9	5
Cough	18	20
Pertussis	16	6
Constipation ..	3	0
Flatulence	0	1
Marked vomiting ..	1	1
Bronchopneumonia ..	1	2
Gastro-enteritis ..	1	1

that a slight rise in intra-abdominal pressure would readily lead to umbilical protrusion. In a few cases the child had an attack of pneumonia or severe bronchiolitis in the first month of life and the hernia followed immediately after the illness. Fig. 5 emphasizes an increased tendency for a hernia to appear during the winter months.

Pertussis. This was a frequent cause. The severe cough and straining can be expected to raise the intra-abdominal pressure sufficiently to cause a hernia. Infective illness in a small child also lowers the muscle tone. In three cases a small hernia had been previously noted and had apparently undergone a clinical cure, but the attack of pertussis caused its reappearance.

Feeding Difficulties. Feeding difficulties and intestinal disturbance appeared occasionally to be the cause of a hernia. Crying due to underfeeding and aerophagy was sometimes evident, and once there was a history of frequent vomiting. Constipation may be either a cause or a symptom of the umbilical hernia and in each of four cases the hernia persisted after 2 years of age. Possibly a general state of sub-nutrition and hypotonia were the cause both of the constipation and the hernia. Two infants had severe gastro-enteritis necessitating hospital treatment during the first few weeks of life, and a hernia was noted immediately afterwards.

Thus illness causing a rise in intra-abdominal pressure may initiate herniation through a baby's relatively insecure umbilical orifice, and an illness or infection, which lowers the general physique causing hypotonicity, may create a background favourable to the development of an umbilical hernia.

Conditions Associated with Umbilical Hernia

Certain definite conditions are associated with umbilical hernia.

Mongolism. Umbilical hernia is commonly present in mongolism, and it may be an associated sign related to the hypotonicity. Over a period of years about 50 mongols have come under my personal supervision and many, but not all, have had umbilical hernia. In each instance the hernia has disappeared spontaneously as in normal children. None required operation or persisted.

Cretinism. Similarly in cretinism an umbilical hernia is frequently seen and may again be related to severe hypotonia. Of 11 cretins personally seen, eight had had umbilical hernia. Six of these umbilical hernias had disappeared under thyroid treatment, and a case is shown in Fig. 6. Three cretins now over 7 years of age have never had an umbilical hernia.

Other Conditions. Umbilical hernia may be present in other conditions leading to a poor

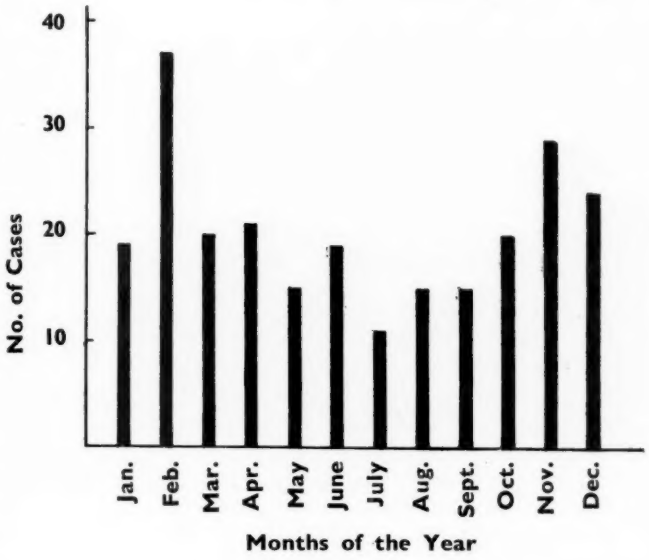


FIG. 5.—The month of year at which hernia first noticed in 225 cases where the parents' statement was known to be accurate.

(*a*) (*b*) (*c*) (*d*) (*e*)

FIG. 6.—A cretin, showing how the umbilical condition cleared under thyroid treatment with no strapping.

physique and may be associated with congenital defects. Recently observed examples include umbilical hernia associated with congenital cataract, with congenital heart disease, with hypospadias, with spina bifida and myelomeningocoele and with gargoylism.

Symptoms

In this series of 283 cases of umbilical hernia there was no apparent disability in the baby. All observers were in agreement with the mothers that the hernia was causing no feeding difficulty, loss of weight, intestinal disturbance or pain. The children were in good health and full activity. Even the two very large hernias, one of which is shown in Fig. 4 gave rise to no symptoms.

Among 143 cases referred to hospital for consultant opinion symptoms were absent in all but five. Four of these mothers stated that the child complained of pain around the navel, but one mother thought it was due to constipation. One mother blamed a tiny hernia for severe vomiting and abdominal pain which occurred periodically, and this child was operated on without delay, but without relief of the symptoms. Henry (1941) states that severe abdominal catastrophe may cause pain apparently referred to a small umbilical hernia and so give the impression that the umbilical hernia is causing the symptoms. But in the few cases where the umbilical hernia was blamed for abdominal symptoms the cause was almost invariably elsewhere.

In one child aged $2\frac{1}{2}$ years a protrusion appeared suddenly through the umbilical orifice four days before the first attendance at hospital. The protrusion had caused pain and vomiting, and on examination there was a tender mass, presumably a small portion of omentum nipped in the orifice. Operation cleared the symptoms and signs. Anatomically this appeared to be of the so-called adult type of hernia in which the hernial protrusion was directed down the umbilical canal and may be an example of the 'semi-umbilical' hernia mentioned by Browne (1952).

No example of strangulation was seen in any of these 283 cases. There is no record of a case of strangulated infantile umbilical hernia in Bristol hospital records.

A child may play with and apply traction upon its own umbilical hernia, and if the hernia is markedly protuberant other children in the family may remark about it. Fig. 7 emphasizes this possibility. For this reason surgical treatment may be demanded by the parents.

Treatment

Careful consideration must be given to the treatment of a condition which is causing no symptoms and rarely gives rise to complications or future trouble. Strapping with adhesive plaster is frequently advocated but it is not without its disadvantages. If the umbilicus has not completely healed sepsis can occur under the strapping and an angry purulent condition of the umbilicus may be found. Two cases were seen. Impetigo develops in the damaged skin occasionally. The strapping is undoubtedly irritating to some babies and may be the cause of frequent crying.

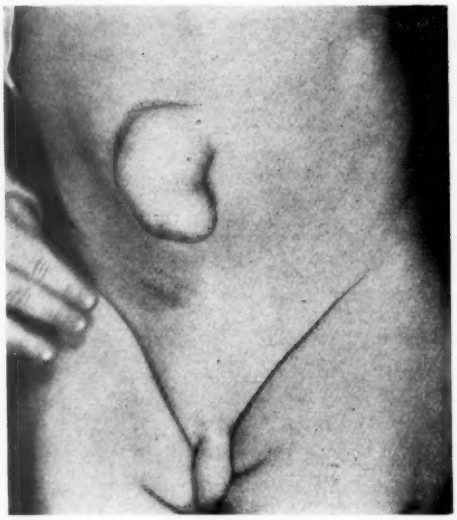


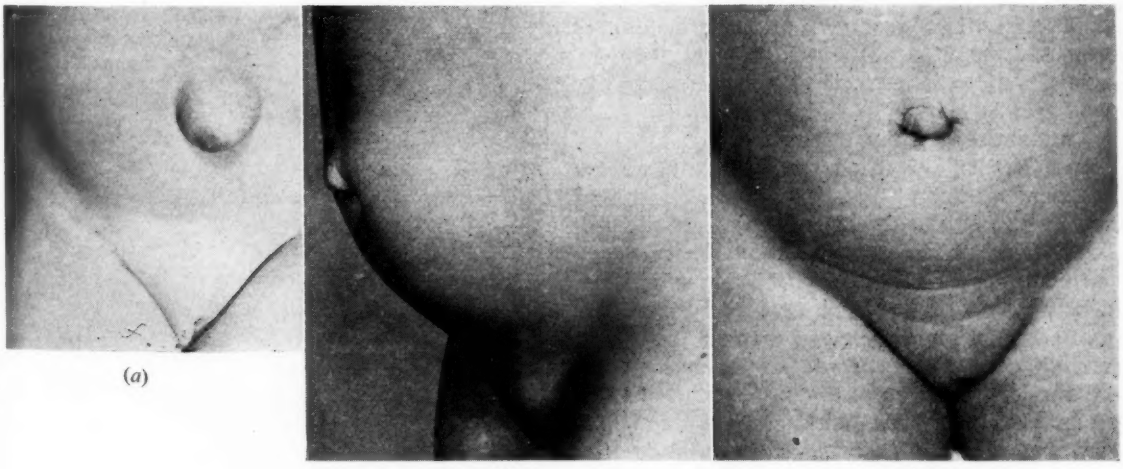
FIG. 7.—A.B., aged 11 months, a poor physical specimen, who had congenital absence of right external auditory meatus. Umbilicus was strapped from birth to 6 months of age. Defect in the linea alba was fairly small. Operated on at 11 months.

Trusses are designed to prevent the protrusion of the bowel into the hernial sac, supposedly by the pressure of an inflated rubber cushion.

On anatomical grounds these methods can hardly be defended. Forcible apposition to the two rectus muscles will not alter the actual size of the umbilical orifice and cannot accelerate a cure which is not already taking place naturally. Richet made this observation in 1856. It is highly important to note that a restriction on the normal activity of the abdominal muscles tends to cause loss of tone and a general ballooning of the abdominal wall. In fact, some children after a long period of strapping or the use of a truss have an anterior abdominal wall resembling in shape and tone the abdominal wall of a multipara (Fig. 8). Strapping may, therefore, have a very significantly deleterious effect. Trusses act in exactly the opposite way, the rubber cushion separating the internal edges of the rectus muscles and tending, contrary to common hypothesis, to enlarge the umbilical orifice and make an automatic cure less likely.

The common absence of symptoms or sequelae and the common finding of spontaneous cure even up to 5 or 6 years of age make the call for surgical treatment rather problematic. In some cases of long-protuberant hernia, with which the child can interfere and play, it may be justifiable to operate. The only cases of long-protuberant hernia in this series have been in children who had persistent umbilical strapping applied. I believe that if the condition was left and no strapping applied at any time this type of umbilical hernia in infants would not occur and certainly the child's attention would not be drawn to it.

For the past three years my policy has been to leave these umbilical hernias alone and wait for a spontaneous cure. A planned experiment to treat alternate cases with strapping and without strapping proved impossible to carry out. A mother whose baby was strapped finding another baby being cured spontaneously without strapping would soon

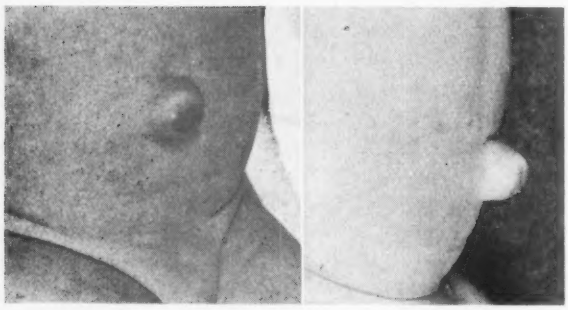


(*a*) (*b*) (*c*)

FIG. 8*a*.—A premature baby, breast fed, aged 11 months. This umbilical protrusion had been continuously strapped since 1 month of age. The hernia protrudes through the superior edge of the umbilical orifice. The condition improved after strapping was stopped.

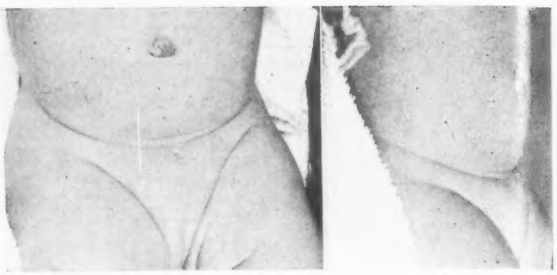
FIG. 8*b*.—Child aged 3 years. Hernia well on the way to automatic cure, and umbilical orifice now barely palpable. Abdominal muscles lax and flabby. No symptoms. Baby brother had a large umbilical hernia, which was cured in seven months with no strapping.

FIG. 8*c*.—Lateral and anterior view in a child aged 3 years.



a *b*

FIG. 9*a* and *b*.—Healthy breast-fed baby aged 5 weeks with umbilical hernia.



c *d*

FIG. 9 *c* and *d*.—Same baby four months later, healthy, still breast fed. No treatment whatsoever was given for umbilical condition.

remove the strapping. On the other hand, at the beginning of the investigation some mothers could not be persuaded not to apply strapping. In some cases strapping had to be discontinued because of the condition of the skin. For the last two years all members of my infant welfare clinics, health visitors, clinic nurses and mothers have been so convinced that strapping is not necessary that the method has been quite abandoned.

The last 122 umbilical hernias seen at the infant welfare clinic have not been treated in any way. All but three have made an automatic cure with complete absence of a peritoneal sac or pulsation on coughing. The three outstanding cases are well on the way to a natural cure.

Of the 132 cases of umbilical hernia over the age of 1 year sent for consultant opinion, 124 had been strapped for a considerable period—some as long as six years. Of the eight that had not been strapped, four became cured spontaneously while under observation. In the remaining four the hernia did not appear until the child was over a year old and may, based on anatomical considerations, have been the adult type of hernia.

In comparison with 122 untreated cases of umbilical hernia, 26 cases from infant welfare clinics were strapped for periods of one month or over. Fifteen of these 26 cases became cured automatically fairly quickly, but five spontaneously only after three and a half to six years. Three children aged between $3\frac{1}{2}$ and 4 years have not yet become normal and three have received surgical treatment.

Possibly comparison should be made between severe and less severe cases to compare the effect of strapping. However, when first seen at the infant welfare clinic soon after birth, no case could be truly called severe. The gap in the orifice felt by pressure varied in size from about 2 mm. to the size of the thumb. The size of the sac and the amount of protrusion were not proportional to the size of the orifice. There might be considerable protrusion through a small orifice and very little protrusion through a large orifice. Forty-nine of the cases that were not strapped had a palpable umbilical orifice as large as the tip of a little finger and all became cured spontaneously. Two cases are illustrated in Figs. 9 and 10. Of 14 cases where the orifice was of similar size and which were strapped, five hernias have not completely disappeared in spite of the fact that the children have reached 3 years of age.

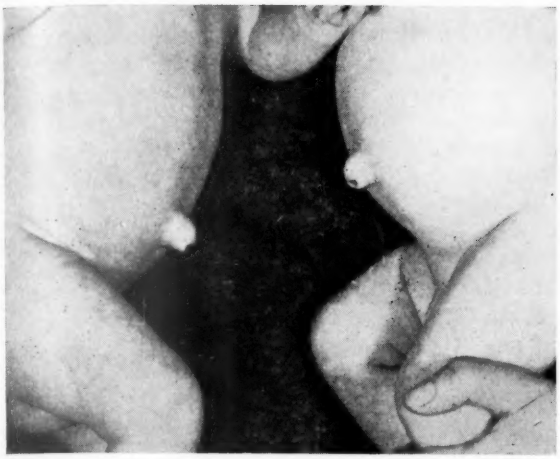
The negro baby with the very large umbilical hernia (Fig. 4) was initially seen at a few weeks of age and a record was made that the orifice was 3 mm. in size and the protrusion was small. The baby was regularly strapped for a year and the size of the orifice and the hernia increased rapidly. Exactly similar events took place in the case of a large hernia in a white baby, who eventually required operation. None of the hernias that were not strapped reached any large proportions and this was also true of the hernias in the other two negro babies. The opportunity arose to strap one and leave one of two

a

FIG. 10*a*.—Healthy breast-fed baby aged 2 months.

FIG. 10*b*.—Condition of umbilicus three months later. No treatment.

b



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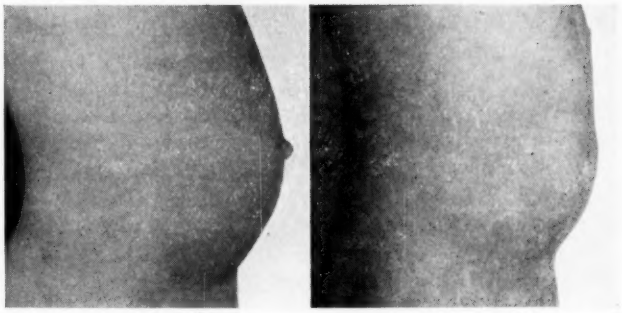

b *c*

FIG. 11*a*.—D.P. and S.P., identical twins aged 2 months.

FIG. 11*c*.—S.P. was never strapped. At 2½ years of age cure is nearly complete.

FIG. 11*b*.—D.P. was strapped or trussed for eight months. Now aged 2½ years cure of umbilical hernia is not complete.

identical twins. This procedure could only be continued for about eight months as the child who was strapped developed impetigo in the area of strapping. It can be seen from the Fig. 11 that (although both children are of poor physical status) the child whose umbilical hernia was not strapped reveals more advanced healing.

In 17 cases from infant welfare clinics that had not cleared by one year of age, 10 had been strapped. Three of those children who had not been strapped had had a severe attack of pertussis which apparently only delayed the automatic cure. Three others who came from poor homes had had several attacks of bronchitis, but despite this, and in the absence of treatment for the hernia, a natural cure is proceeding. One healthy little boy made a perfectly satisfactory cure by 20 months. The clinical emphasis is strongly against strapping.

In many cases where the parents expressed a desire for operation the baby's name was placed on the waiting list. Owing to shortage of beds there was frequently an interval of several months before the baby was admitted to hospital and in this interval, and in the absence of any form of treatment, spontaneous cure had frequently occurred. During the course of these investigations long-term observations were made on a series of nine cases. Four cases were followed up and found to be cured by 5 years of age, two were cured by 6 years, two by 7 years and one by 8 years of age.

Incidence

As already mentioned, the incidence among 573 healthy babies seen at infant welfare clinics was 1 : 5·4. The high incidence of umbilical hernia in infants might suggest that nature would design a cure.

An opportunity arose to note the incidence in nursery school children. Ten very small herniae, all in children aged 2 years, were found among 105 children in one school. All had cleared before the children left school at 5 years. This relatively high incidence may have been related to the practice of recruiting children for nursery schools from homes where maternal care and circumstances are unfavourable. The healthier life in a nursery markedly improved the muscular tone of these children and may have been responsible for an accelerated cure. In another nursery school, among 300 children aged between 3 and 5 years no hernia was found.

Among 250 school children aged 5 to 11 years personally examined, five hernias only were noted. Four were very small and one was large and this had been strapped for six years. Two half-caste children had been operated on for umbilical hernia in infancy. In another survey of approximately 3,000 school children aged between 5 and 18 years only three umbilical hernias were found, and one of these became cured spontaneously in the following few months. These very few hernias in older children were causing no morbidity. Routine examination of 800 university students showed no evidence of umbilical hernia. This suggests that the ultimate residuum of infantile umbilical weakness or abnormality in the population is negligible.

Discussion

From the evidence available in this investigation and from consideration of the anatomy, it would appear that a patent orifice at the umbilicus is present for some time after birth and can be regarded as normal. The size of the orifice may vary from a minimum of 1 mm. to the dimensions of an adult thumb. The observation that the fascial strengthening of the umbilical region has not fully developed in the early months of life offers a simple explanation for the occurrence of a small hernia through the umbilical orifice even in a perfectly healthy infant.

The anatomical state can be regarded as no more than a variation within the normal.

The occurrence of an umbilical hernia in a particular infant might be related to difference in embryological, anatomical and inherited make-up, and with the normal growth of the baby the umbilical fascia develops to an extent which will bring about the spontaneous disappearance of the hernia.

Conditions which contribute to under-development or late maturation of the fascia of the abdominal wall, or a particular weakness of this fascia, or a marked hypotonicity of the abdominal muscles, will increase the incidence of umbilical hernia, or aggravate the condition when present and delay a spontaneous cure. Thus deficiency in the local fascia is particularly demonstrable in premature infants and in these children umbilical herniae occur with greater frequency. Umbilical sepsis has been observed as a contributory factor in the development of hernia. In upper respiratory infection or any general infection umbilical hernia is more likely to develop or to show delay in natural cure. Conditions such as mongolism and cretinism are classically related to umbilical hernia and indicate that umbilical hernia is more likely to appear in disease of which muscular hypotonicity is characteristic.

From the observations recorded in this paper there appears to be little doubt that in the healthy baby umbilical hernia has a very strong potentiality for spontaneous disappearance. In the present survey 93% of children became cured automatically in the first year of life in the absence of any strapping or truss. There is considerable evidence that the local application of restrictive appliances may actually delay the disappearance of the hernia or even increase its severity, perhaps because the limitation of spontaneous and free movements of the abdominal musculature inhibits stimulus to local anatomical maturation.

Conclusions

Two hundred and eighty-three infants with umbilical hernia have been studied. In this series a frequency of an umbilical hernia of one in six infants has been recorded. The first appearance of the hernia is usually within the first few months of life and rarely after six months.

The incidence of herniation after premature or twin births is significantly higher than after a normal birth.

Breech births, babies of high birth weight and babies whose cords are of unusual length appear somewhat more predisposed to umbilical hernia. Mild sepsis of the umbilicus after separation of the cord is related to an increased tendency to herniation.

Granulation tissue forming at the umbilicus prevents herniation.

Umbilical hernia is compatible with normal healthy growth and its occurrence is, in part, dependent on the child's inherited status. Constitutional conditions causing either hypotonicity of the abdominal musculature or a rise in the intra-abdominal pressure favour the development of a hernia and aggravate the condition if present.

In infants symptoms directly attributable to umbilical hernia are rare and no case of strangulation has been recorded.

Spontaneous cure is a very common event. The use of restrictive appliances such as strapping and trusses frequently aggravate the condition and delay a spontaneous cure.

The ultimate incidence in school children and early adult life is very small.

In a prolonged investigation of this type, I have received help from many sources. I would particularly wish to thank Professor A. V. Neale, at whose suggestion this investigation was carried out, for detailed assistance in the preparation of this paper, and Mr. W. A. Jackman, who allowed me to obtain the details from his out-patient cases over a period of years and Professor R. H. Parry for permission to use the facilities of the infant welfare clinics. My thanks are also due to Dr. G. Herdan for statistical help, to Dr. A. A. Craig and Dr. S. W. Terry for obtaining the figures from school children and Dr. D. E. Oliff for the figures from university students. I wish to thank the general practitioners who allowed me to pay domiciliary visits to their patients and the health visitors who gave full and willing cooperation.

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INVOLUTION OF THE LEFT LIVER IN THE NEWBORN AND ITS RELATIONSHIP TO PHYSIOLOGICAL ICTERUS

BY

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It was recently shown (Emery, 1952) that in approximately a third of children dying within the first few days of birth there was microscopic evidence of degeneration of parenchymal cells in the left physiological lobe of the liver. This change was not seen in stillborn children and was seen with increasing rareness in older children. It was suggested then that the changes were due to cessation of the flow of placental blood through the left liver at birth.

The importance of the microscopic changes in the liver should be reflected in gross changes in size of the different lobes of the liver at birth, and the present communication records a study of gross changes in the liver associated with birth.

Materials and Methods

The material consisted of the livers from a consecutive series of 100 necropsies on premature stillborn infants and children dying within the first 12 weeks of birth.

Owing to the high incidence of fatty and other changes in the right liver associated with intra-uterine anoxia and placental disease found in mature stillbirths, it was felt that such livers could not be taken as representative of the normal liver at the time of birth. For this reason mature stillborns were excluded from the series reported here.

The livers were removed from the body with minimal manipulation and, after examination of the gall-bladder and ductus venosus, the liver was divided into two parts along the line of division of the physiological left and right lobes (Cantlie, 1898; Mall, 1906). The cut was made through the mid-part of the attachment of the gall-bladder to the liver. The anterior edge of the liver was cut directly opposite the tip of the gall-bladder and the incision carried obliquely backwards to the most anterior aspect of the hepatic vein where it entered the vena cava. The cut surface so produced is almost bloodless in contrast to that resulting from cuts in other parts of the liver.

The lobes were then weighed and the ratio of the weight of the right to the left lobe obtained, i.e. the right lobe weight was divided by the weight of the left lobe.

The maturity of the premature stillborns was assessed by a combination of the known date of the mother's last menses and the crown-rump length of the infant based on the data of Scammon and Calkins (1929) and Streeter (1920).

Results

The average ratio was found to be constant in the last few months of intra-uterine life, the ratio being 0·89, i.e. the left lobe being about a tenth larger than the right (Table 1). The ratio was found to be unchanged in children dying within 12 hours of birth.

TABLE 1

THE RATIO OF THE WEIGHTS OF THE RIGHT AND LEFT LIVERS IN INFANTS OF DIFFERENT AGE GROUPS

Age of Child	Ratio of R.:L. Lobes	Number of Cases
5 to 7 lunar months	0·89	7
8 lunar months	0·87	6
9 lunar months	0·89	6
Birth to 12 hours ..	0·89	14
13 to 24 hours ..	1·00	3
25 to 48 hours ..	1·04	9
3, 4 and 5 days ..	1·02	10
6 to 14 days ..	1·16	13
15 to 21 days ..	1·11	7
3 to 6 weeks ..	1·12	11
7 to 12 weeks ..	1·14	14
	Total	100

Within 48 hours of birth a marked change in ratio of the lobes occurs, the right lobe becoming larger than the left; the ratio thus becomes almost exactly the reverse of the foetal ratio. This change is completed by the end of the first week. From this time the ratio of the lobes throughout the rest of early infancy seems to remain fairly constant. This rapid change over in dominance of the left lobe *in utero* to the right lobe in early infancy is illustrated graphically in Fig. 1.

For the purpose of statistical study the cases were grouped as in Table 2 and analysed on the numbers of livers showing right lobe preponderance. The change over in dominance of the lobes was significant ($\chi^2=38{\cdot}62$) and the probability of the findings being due to chance less than one in a thousand.

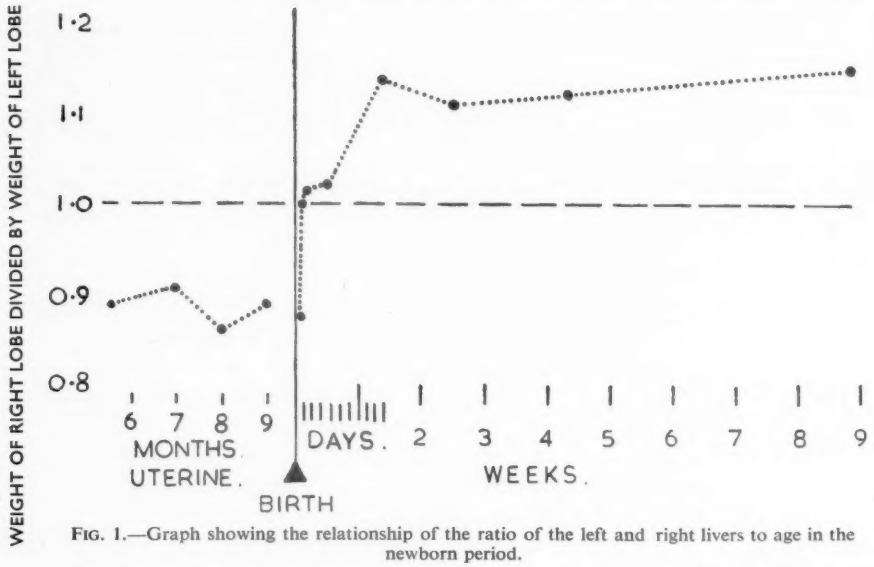

FIG. 1.—Graph showing the relationship of the ratio of the left and right livers to age in the newborn period.

Discussion

Taken in conjunction with the previous observations (Emery, 1952) of microscopic evidence of degeneration of parenchymal cells in the left liver, it seems that we have irrefutable evidence that following birth there is a rapid involution of the left liver. This involution is apparently completed by the end of the first week of extra-uterine life. The delay of about 12 hours after birth for gross changes in weight of the left liver to be seen seems to be simply a lag between the onset of degeneration and the gross evidence of its occurrence.

Much of the literature relating to the vascular changes occurring at birth has been discussed previously in connexion with the microscopic evidence of cell degeneration in the liver (Emery, 1952), and this will not be repeated here. In brief, the change seems to be directly consequent upon two factors, one, the sudden cessation of perfusion of the left liver by blood direct from the placenta, and second, the transitory persistence after birth of patency of the ductus venosus which permits the temporary existence of a potential Eck fistula. Of these two factors the first is of predominant importance.

Blackfan (1933) in the White House Report states that the involution of the left liver takes place before birth. Arey (1946) remarks, concerning the late intra-uterine state, that 'in certain regions the hepatic tissues undergo degeneration (due to pressure atrophy) and especially is this true of the left lobe'. These statements are probably based upon measurements of the livers of mature stillborn infants before the fatty and hydropic changes consequent upon intra-uterine anoxia (Gruenwald, 1949) were realized. The finding in the present series that the livers in the first few hours of life are similar to those before birth suggests that the changes in the left livers are postnatal and due to changes occurring at birth.

Ruge (1908), in discussing the external morphology of the foetal liver, noted that the left anatomical lobe was within a centimetre of the size of the right anatomical lobe, and that after birth the left lobe became smaller. Keibel and Mall (1912) noted a temporary relative decrease in the size of the whole liver at birth, i.e. a temporary interruption of the growth of the liver. They considered, as do others, that the changes in the size of the lobes of the liver were due to the pressure of adjacent organs, in particular the stomach. This explanation does not seem likely, as it is difficult to imagine how the pressure of different freely movable organs within the abdominal cavity could be different in different parts of the lower surface of the liver.

TABLE 2

NUMBER OF LIVERS IN DIFFERENT AGE GROUPS RELATED TO SIZES OF PHYSIOLOGICAL LEFT AND RIGHT LOBES

	Immature Stillborns	Birth to 12 Hours	25 Hours to 12 Weeks
Livers with R.:L. ratio greater than 1	3	4	53
Livers with R.:L. ratio less than 1	16	10	11
Total number of livers in group	19	14	64
Percentage of group with R. liver greater than L. liver	15·7	28·6	82·8

The chief interest in the involuting changes in the newborn lies in the relationship to the production of physiological icterus. Our knowledge of physiological icterus has recently been well discussed by Smith (1951). He appears compelled to consider what is in effect 'physiological immaturity' of the liver as the major factor, and the statement by Davidson, Merritt and Weech (1941) that 'the degree of hyperbilirubinemia is a measure of the functional maturity of the infant at the time of

birth' he refers to as the 'omega' of our present knowledge.

It can hardly be without significance that the same period after birth, i.e. about 100 hours, when the left liver is in a state of partial necrosis, is exactly the same as Yudkin, Gellis and Lappen (1949) found by bromsulphalein excretion tests when the liver showed its most grossly impaired function. The acute involution of the left liver after birth seems to be a reasonable explanation of the transitory inadequacy of the liver seen in the first few days of life. This would provide the most satisfactory explanation available at the moment of the post-natal rise in the bilirubin level and of the development of jaundice after birth.

Although the details of the mechanism do not appear to have been studied, the idea that icterus neonatorum is related to circulatory changes in the liver is by no means new. The following extract from a translation of a treatise on 'Disease of the Liver' by Frerichs (1860) written almost a hundred years ago is relevant.

> 'The mode of production of icterus neonatorum in ordinary cases must be sought for in the diminished tension of the hepatic tissues, which takes place upon the stoppage of the influx of blood from the umbilical vein.'

The post-natal vascular changes in the liver will not explain the presence in a number of infants of a raised bilirubin level in the cord blood at the moment of birth (Davidson *et al.*, 1941). A raised bilirubin level in the cord blood is known to be associated with an enhanced post-natal rise in bilirubin level and thence with an increased incidence of clinical icterus. In many instances physiological icterus follows a normal bilirubin level in the cord blood and thus there seem to be two separate factors, one post-natal and the other ante-natal. The most likely site of the ante-natal factor is the placenta. It is known that placental changes affect the foetal liver (Gruenwald, 1949) and Williamson (1923) found an increase in placental iron parallel with the increase in bilirubin in the cord blood. This aspect is at present under investigation and will be reported later.

Summary

There is a rapid involution of the left lobe of the liver beginning just after birth and completed within four or five days of birth.

This involution seems to be the direct result of changes in blood supply to the liver associated with birth.

The involution of the left liver coincides with the known period of deficient functional activity of the liver in the newborn. It is probably the cause of the temporary hepatic inadequacy during the first few days of life, hence the cause of the post-natal rise in bilirubin level associated with physiological icterus.

It is a pleasure to be able to acknowledge the courtesy of Dr. Warrack, in permitting facilities for much of the material reported in this study, and Miss C. Roseman for help with statistical interpretation.

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THE PATTERN OF HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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Maternal immunization against the Rh factor may result in intra-uterine death of the foetus or hydrops foetalis, which we have called severe forms of the disease, or in icterus gravis, with or without kernikterus, or a haemolytic anaemia without obvious jaundice, and these we have called mild forms of the disease. It is frequently assumed that in any one family successive Rh-positive infants tend to be progressively more severely affected (Allott, 1951; Diamond, 1950; Ellis, 1951; Salomonsen, 1952; Sheldon, 1951; Whitby and Newns, 1953) and though this is sometimes true it is not entirely in accord with our experience. In most of the families we have studied, the affected offspring have all been mild cases, but in other families they have all been severe cases; a small proportion of families have contained cases of both kinds. This concentration of the severe cases into a small proportion of the families is well illustrated in a consecutive series of 103 'Rh families' at the Birmingham Maternity Hospital, in which four-fifths of the severe cases occurred in only one-fifth of the families. By contrast in the whole of the material at our disposal more than three-quarters of the families contained no severely affected case.

Material

Our material has been drawn from several sources: from the Birmingham Maternity Hospital, from the maternity department of Dudley Road Hospital together with other maternity hospitals in Birmingham where replacement transfusions have been performed in the last three years, and from the Birmingham Children's Hospital. We have studied 440 families made up as follows:

Birmingham Maternity Hospital. From 1949 to 1953, 103 families, in which Rh iso-immunization had occurred, formed a consecutive series, whether the infant was viable at birth or not.

Dudley Road and Other Maternity Hospitals. From 1950 to 1953, 114 families, not consecutive, were selected by the fact that in nearly every family one infant had been given a replacement or simple transfusion.

Birmingham Children's Hospital. From 1927 to 1953, 223 families, in which at least one child had received treatment for haemolytic disease at the Children's Hospital were studied.

Method of Study

The families in each group have been sub-divided into those 'mild' families in which the first child affected with haemolytic disease was a mild case by our definition, i.e., icterus gravis (with or without kernikterus) or haemolytic anaemia, and those 'severe' families in which the first affected was stillborn or hydropic, classed as severe forms. The incidence of the mild and severe forms of the disease in infants born subsequently has then been analysed, and the details of this analysis are presented in Table 1. We have in this table assumed that every stillbirth was due to Rh iso-immunization. We have classified as miscarriages and abortions all deliveries before the twenty-eighth week of pregnancy; the higher incidence of these in the severe group of families suggests that some at least may have been due to Rh iso-immunization.

Results

It is evident from Table 1 that the three mild groups all show a similar pattern. Thus, if the first affected child is a mild case, the ratio of mild to severe among subsequent children is 9 to 2. The three severe groups, however, are not so homogeneous and this was not unexpected: the Birmingham Maternity Hospital cases are an unselected consecutive series, the Birmingham Children's Hospital are predominantly mild cases because of the selection of families including at least one mild case, and the Dudley Road and other maternity hospitals cases form an intermediate group. Of these three, therefore, the Birmingham Maternity Hospital cases are probably the most reliable on which to base

prognosis, whence, if the first affected is a severe case, the ratio of mild to severe among subsequent pregnancies is 1 to 2. Thus the chances that the next affected will be a severe case are considerably greater if the first is a severe case than if it is mild.

Two further considerations, each tending to decrease the number of subsequent severe cases in the severe group, must be taken into account. (1) Some families belonging more properly perhaps to the mild group are classed as severe on an early stillbirth possibly not due to Rh iso-immunization; to this we have already referred as deliberate policy. (2) In some women, already known to have produced Rh stillbirths, pregnancy has been induced early with the production of a viable child with no more than a mild form of the disease. In an attempt to eliminate bias due to these circumstances we have selected 15 families in which the first affected was hydropic or stillborn and known to be due to Rh iso-immunization. Of subsequent offspring delivered at term, two were unaffected (Rh negative), two were mildly and 19 were severely affected. The ratio of mild to severe is now 1 to $9\frac{1}{2}$, or in these families, of viable to non-viable in pregnancies subsequent to a known 'Rh severe' case, 2 to $9\frac{1}{2}$, almost exactly the inverse of the ratio found in 'mild' families.

Table 1 shows that the differences in the average number of children per family between the six groups are not very great, although in computing these figures we have included as 'children' all those pregnancies terminating in stillbirths or abortions, in addition to live births. But when the total is analysed into the mean numbers before and after the first affected, it will be seen that 'severe' families have on an average from two and a half to three times as many children after the first affected as do 'mild' families; in fact, 64% of the 'mild' families have no further children after the first affected, compared with 16% of the 'severe' families. In the remaining 'mild' families, however, 83% of the next pregnancies to the first affected and 60% of the next but one, produced mildly affected children, the corresponding figures for severe families being 43% and 56%. The last figure may be somewhat inflated because of the inclusion of several children born after premature induction of labour: in the 15 selected families referred to above, the percentages of mild cases in the next and the next following pregnancies are only 20% and 0% (five cases only) respectively.

This confirms our original suggestion that one group of mothers tends to have infants with mild forms of the disease and that even their second and third affected are predominantly mild, while the other, smaller group of mothers tends to have severely affected infants. Allen, Diamond and Vaughan (1950) have stated that of second affected infants 40% are stillborn, which would suggest that there is a rapid increase in the severity of the disease in successive affected offspring. This increase, however, is more apparent than real because it is the severely affected mothers, rather than the mildly affected, who are most productive. That 'severe' families in general have nearly three times as many subsequent pregnancies as 'mild' families accords with the common obstetric experience that a succession of stillbirths acts more as a stimulus than a deterrent in many families eager for living children of their own.

Possible Aetiological Factors

Table I shows the additional and important fact that severely affected mothers have fewer children than mildly affected mothers before their first affected child. From this we may surmise that severely

TABLE 1

AN ANALYSIS OF FAMILIES ACCORDING TO THE SEVERITY OF THE DISEASE IN THE FIRST AFFECTED CHILD

	Hospital Group	No. of Families	Previous Pregnancies*	1st Affected	Subsequent Children					Total Children	Children per Family		
					Total No.	Affected		Normal (%)	Miscellaneous and Abortions (%)		Average No. per Family	Children before 1st Affected	Children after 1st Affected
						Mild (%)	Severe (%)						
Mild	B.M.H.	80	181	80	60	70·0	21·7	5·0	3·3	321	4·01	2·26	0·75
	O.M.H.	99	198	99	38	73·7	15·8	7·9	2·6	335	3·38	2·00	0·38
	B.C.H.	197	413	197	165	67·8	12·2	13·9	6·1	775	3·93	2·10	0·84
Severe	B.M.H.	23	29	23	42	23·8	47·6	7·1	21·4	94	4·09	1·26	1·83
	O.M.H.	15	27	15	39	33·3	30·8	23·1	12·8	81	5·40	1·80	2·60
	B.C.H.	26	35	26	54	55·6	16·7	16·7	11·1	115	4·42	1·35	2·08

* Including miscarriages and abortions (i.e. all deliveries before 28th week of pregnancy).
B.M.H. = Birmingham Maternity Hospital. O.M.H. = Dudley Road and other maternity hospitals.
B.C.H. = Birmingham Children's Hospital.

affected mothers are more readily sensitized than mildly affected mothers, and this susceptibility to sensitization results in the earlier onset and greater severity of the disease in this group.

We have also investigated the incidence and distribution of several other serological properties:

The Titre of Rh Antibody in the Maternal Blood. This was known in 142 deliveries (94 mild and 48 severe), and is shown diagrammatically in Fig. 1. Low, intermediate and high titres may be associated with any manifestation of the disease, with the exception that we found titres above 1 in 512 only when the foetus was hydropic, stillborn or, more remarkably, Rh negative. It seems likely that the titre may rise excessively when the foetus is unable to adsorb antibody (Arnold, Walsh and Herzger, 1951), i.e. when it is dead, saturated (hydropic) or Rh negative.

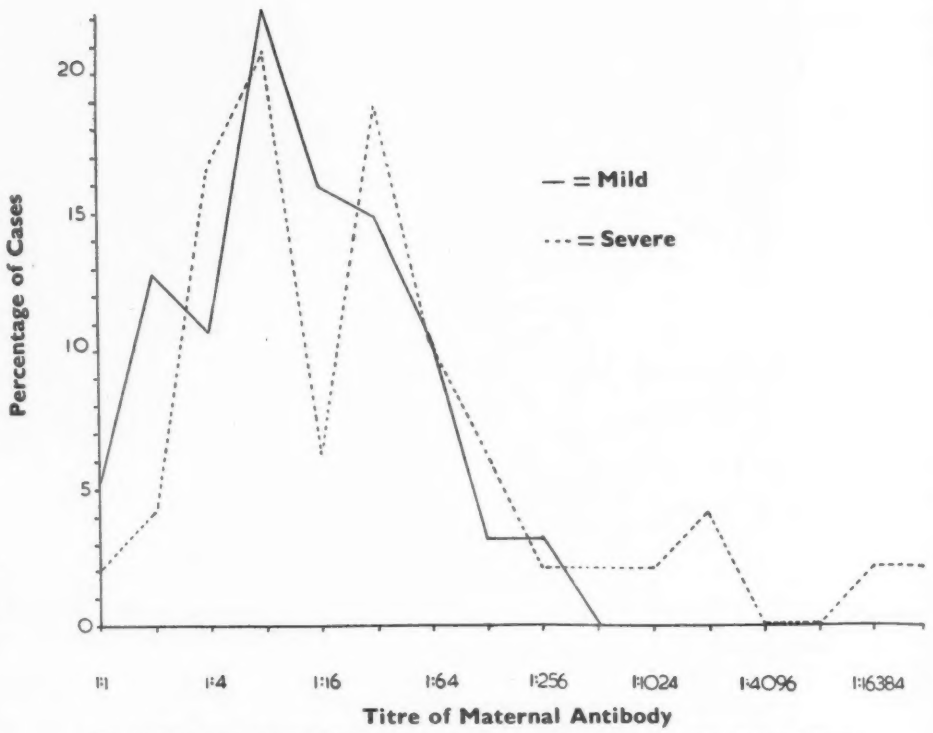

FIG. 1—The maternal antibody titre near term in 94 mildly and 48 severely affected infants.

Non-Homologous Rh Blood Transfusions to the Mother. The incidence of these was analysed only in the Birmingham Maternity Hospital and Dudley Road and other maternity hospitals groups where our data were adequate, and the results are shown in Table 2.

TABLE 2

INCIDENCE OF RH-POSITIVE BLOOD TRANSFUSIONS SENSITIZING RH-NEGATIVE MOTHERS

	Mild	Severe
Total number of mothers	179	38
Number transfused with Rh-positive blood ..	14	11
Percentage receiving transfusions of Rh-positive blood	7·8	28·9

The proportion of mothers in the severe group who had been transfused with Rh-positive blood is more than three times that found in the mild group. This is a highly significant difference, and it seems therefore that such transfusions may sometimes dislodge a woman from the mild to the severe group, but this factor accounts at the most for not much more than a quarter of the cases in the severe group.

The ABO Groups of the Parents. The parents of children with haemolytic disease are compatibly mated on the ABO system more frequently than would be expected (Levine, 1943), i.e. if the Rh grouping were to be ignored, the father could be a donor to his wife in more instances than would occur in random matings. The distribution of the known ABO grouping in our cases is shown in Table 3.

TABLE 3

THE PERCENTAGE DISTRIBUTION OF ABO GROUPS IN PARENTS AND AFFECTED OFFSPRING

ABO Group	Mother		Father		Baby	Normal Distribution
	Mild	Severe	Mild	Severe		
O	36·1	32·4	51·8	68·7	42·7	46
A	51·6	56·8	44·6	25·0	45·2	43
B	8·2	10·8	3·6	6·3	8·1	9
AB	4·1	0	0	0	4·0	3
Total	122	37	83	32	124	

The distribution of the ABO groups in affected infants does not differ appreciably from that in the population at large, but there is a shift towards

Group A in the mothers and towards group O in the fathers, i.e. towards compatibility in the above sense. This shift is greatest in the severe group, but it is still obvious in the mild group and by itself does not explain, though it may influence, the incidence of the two groups. Stated in another way, nearly 87% of the fathers, if the Rh group is ignored, could be blood donors (cells to serum) to their wives, while only 61% of the wives could be donors to their husbands (Table 4). The proportion of wives able to give blood to their husbands is in close agreement with expectation in the mild group but differs considerably, though not quite significantly, in the severe group.

TABLE 4
ABO COMPATIBILITY OF PARENTS

Compatibility	Mild Group (%)	Severe Group (%)	Combined (%)	General Population (%)
Husband to wife ..	87·5	84·4	86·6	66·2
Wife to husband ..	66·3	46·9	60·7	66·2
Total numbers	80	32	112	

The Parental Genotype. In an unselected group of Rh-positive individuals approximately 43% are homozygous (DD) with respect to the D antigen, but the proportion is greater among the fathers of babies with haemolytic disease. The actual proportion to be expected depends upon the distribution of family size, and Table 5 shows the ratios calculated on the assumption that the second and subsequent Rh-positive foetuses will be affected. Among families with two children with haemolytic disease the expected ratio of homozygous to heterozygous fathers is about 3:1 (Fraser Roberts, 1951, quoted by Race, 1952), but in families with three children it is 3:2, and thereafter the proportion of homozygotes decreases towards the general population values.

TABLE 5
D-GENOTYPE OF RH-POSITIVE FATHERS OF FAMILIES WITH HAEMOLYTIC DISEASE

Size of Family	Homozygous % Expected
2	75
3	60
4	52
5	48
6	45·7
7	44·4
8	43·6
General Population	42·8

In our material Table 6 shows that the ratio is about 2:1, and, moreover, it is almost identical in both the mild and severe groups, from which we may infer that whatever agency determines the character of the disease in a family it is not closely related to the D-genotype of the father. Also shown in Table 6 is the overall proportion of homozygous (DD) Rh-positive fathers expected in our material, calculated from our family size distribution and Table 5. There is a slight excess of homozygous fathers over the expected figure which may be due to the inclusion of some pregnancies on serological grounds rather than in the way postulated in Table 5.

TABLE 6

	Homozygous (%)	Heterozygous (%)	Total Number
Mild	63·6	36·4	110
Severe	69·7	30·3	33
Expected	57·1	42·9	

Discussion

On the evidence we have presented there seems reasonable justification for the division of families with haemolytic disease into two main groups. The offspring of one are predominantly mildly affected, those of the other are predominantly severely affected, but there are also some intermediate families in which the disease in successive affected infants is more severe. Our analysis has probably emphasized the two extremes of a spectrum.

From the data we have collected it is not possible to predict into which group a woman will fall, but the division into two groups based on the form which the disease takes in the first affected offspring is of prognostic value. If a mother's first affected infant is a mild case, then in 83% of cases her next child will also be mildly affected. The danger of kernikterus can almost always—if not always—be obviated by adequate exchange transfusions (Diamond, Allen, Vann and Powers, 1952) and our own experience (Davies, Gerrard, Hatchuel and Howarth, 1953). But if the first affected child is a severe case the next affected will, in 80% of cases, also be a severe case, if delivered at term. It seems reasonable in these cases (unless the father is heterozygous) to practise the premature induction of labour. This has been done in 10 of our families (11 pregnancies, including one twin pregnancy) and in every case the baby was mildly affected. Induction or Caesarean section has been carried out as early as the thirtieth week, but was usually performed between the thirty-fourth and thirty-sixth weeks of pregnancy. Such a transformation in the outlook for the foetus is not to be

expected every time, but from our material it seems that induction or Caesarean section at the thirty-fifth week might have saved three-quarters of the infants in this severe group (19 out of 25 cases).

The decision when to induce in the individual case can only be taken by the obstetrician, but he may be guided by the mother, who may notice that foetal movements are becoming less vigorous (Watson, 1953), and by the liquor, a rise in the non-haematin iron content being associated with a corresponding anaemia in the infant (Bevis, 1952). When the baby is delivered, either by the natural route or by Caesarean section, and if it has haemolytic disease, it is important that the paediatrician should be prepared to attempt an adequate exchange transfusion (80-100 ml. per lb. body weight) soon after delivery, or to give two smaller exchange transfusions (60 ml. per lb. body weight) should the baby's condition not allow the larger initial exchange. Both lines of treatment have been used with encouraging results.

We are unable to state why there are these two groups, but there are two factors which suggest that the severity of the disease in the infant or foetus is related to the efficiency of the maternal production of antibody. First, the women who have the fewest unaffected infants, and who are presumably the most easily sensitized, are those who have the most severely affected infants, and secondly, the Rh-negative women who have had transfusions of Rh-positive blood, a very powerful antigenic stimulus, also tend to have severely affected infants. It is nevertheless true that the maternal titre of antibody does not clearly reflect the severity of the disease in the foetus, but this is probably because the titre gives no indication either of the quantity of antibody crossing the placenta, or of the quantity taken up by the foetal cells.

Summary

Families containing babies with haemolytic disease of the newborn have been classified into two main groups depending on the gravity of the disease in the first affected baby. If this first affected baby has a mild form of the disease, i.e. is not hydropic or stillborn, then in 83% of cases the next affected will also be a mild case. If this first affected baby is hydropic or stillborn, then in 80% of cases the next affected will also be hydropic or stillborn, if delivered at term.

Women whose first affected baby is hydropic or stillborn have three times as many subsequent pregnancies as do those whose first affected is a mild case; the women who are least likely to have a viable infant endeavour most to obtain one. If such women are allowed to go into labour spontaneously the baby will usually be stillborn or hydropic; it is suggested that, unless the husband is heterozygous, in these cases the premature induction of labour is indicated.

By contrast, women whose first affected baby is a mild case need not necessarily be discouraged from having another infant because affected children born subsequently are usually mild cases also.

The severity of the disease in the foetus appears to be greatest in the offspring of women who have had the fewest unaffected children or who have had transfusions of non-homologous Rh blood, i.e. the disease is most severe in the offspring of women who are most easily sensitized or who have had the most powerful antigenic stimulus.

We are very grateful to Dr. W. Weiner for his help in this study, and to Dr. Frances Braid, Dr. V. Mary Crosse, Mr. H. B. Watson and the many obstetricians and paediatricians who have given us access to their cases.

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DUODENAL ULCERS WITH EXTENSIVE LIVER DAMAGE IN INFANT TWINS

BY

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Peptic ulcer in infancy was first described by Cruveilhier (1829-42) over a hundred years ago, and those who have described cases or series of cases in more recent years (Holt, 1913; Kennedy, 1933; Guthrie, 1942; White Franklin, 1942; Fisher, 1950), and others have usually emphasized the view that the condition may well occur more frequently than is generally supposed. Paterson (1922), however, was able to find only a hundred cases in the literature and only three cases, including two observed by himself, in this country. Most reported ulcers have been in the duodenum.

It seems probable that many cases in which small ulcerations are present will be missed unless a special search is made, and this is perhaps true in some cases of liver disease with haemorrhagic phenomena such as bleeding into the lumen of the gut, in which the exact site of the bleeding is not ascertained.

Haemorrhagic disease of the newborn may be a manifestation of erosion either in the duodenum, stomach or at the lower end of the oesophagus, which normally heals rapidly. In later infancy the clinical picture tends to be more complex and varied than in the newborn period. Many of the reported cases have presented as prolonged and obstinate feeding difficulty leading to a picture of marasmus in which a duodenal ulcer has been found at necropsy. Others have presented the clinical picture of pyloric stenosis in infants of 4 to 6 months or more. The history of pain related to meals does not appear until later childhood.

There are also the cases occurring at various ages in which ulceration appears to be related to cerebral damage or neoplasm, or to infected hydrocephalus, and finally there is the doubtful association with burns (Curling's ulcer).

The association of liver disease with duodenal ulcer was noted by Guthrie in one of her cases in which there was hepatitis, and by White Franklin in the first case in his series in which the liver showed extensive and severe fatty change.

The two cases to be described are unusual in that they occurred at the same time in binovular twins, in an illness of sudden onset associated, as in White Franklin's case, with an extreme degree of liver damage.

Case Reports

Case 1. Jean A. was born on November 1, 1951, a premature twin.

Delivery was normal (birth weight 3 lb. 5 oz.) and feeding began on the third day. At the eighteenth day there was some abdominal distension and a little mucus in the stools, and the infant was given penicillin orally for four days. She made steady but slow progress after this, and was discharged from hospital on January 10, 1952, weighing 6 lb. 10 oz. Breast feeding had failed after the first three weeks, and the baby was taking 'ostermilk'. Home conditions were poor. The parents with two other children aged 10 and 11 and twins aged 18 months lived in a dilapidated agricultural cottage. The family was healthy and there was no family history of peptic ulcer. The progress of the newborn twins at home was satisfactory until February 20, 1952. The feeds had been increased normally and the mother had added a wheat starch cereal ('Neave's food') to the bottle feeds. On the afternoon of February 20, both twins seemed fretful and refused their feeds. They vomited several times and their stools became loose and green. The other twin, Shirley, became dehydrated and seriously ill and was admitted to hospital four days later but Jean, after 24 hours on saline feeds, seemed much better and normal feeding was gradually restored. She still vomited occasionally however and did not appear completely well, and on the night of February 26 she vomited several times and seemed fretful and in pain. The mother noticed a shrill and unnatural cry. She became suddenly very pale and collapsed, and died during the night. There was no jaundice. The body was sent into the Royal Berkshire Hospital the following morning, and a limited necropsy was performed. The organs were exsanguinated and the liver, in addition, was a pale yellow suggesting extensive fatty change. The brain was normal to naked-eye inspection. A large duodenal ulcer was found and the whole gut was filled with dark blood clot. The ulcer was punched out and was situated in the posterior wall of the first part of the duodenum.

FIG. 1.—Photograph of ulcer in Jean A.

FIG. 2.—Section of ulcer in Jean A. ×7.

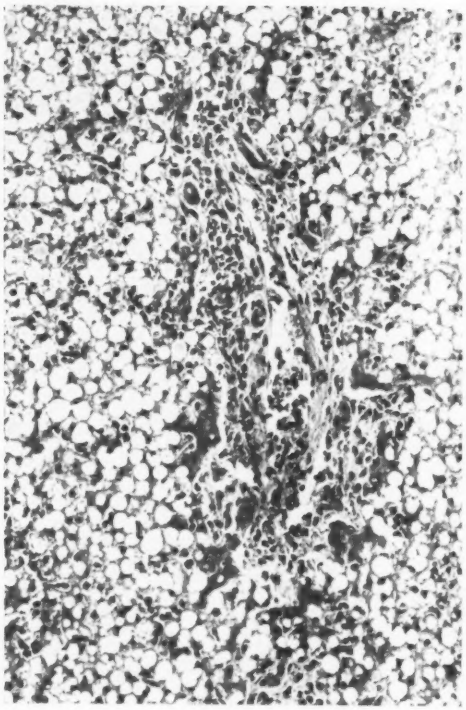

FIG. 3.—Section of liver in Jean A. ×140.

It measured 1·2 by 1 cm. in its maximum diameters, and the base was formed by the head of the pancreas (Fig. 1). Several small thrombosed vessels could be seen at the proximal margin. Microscopy showed the ulcer to be an acute lesion penetrating all coats except the serosa overlying the pancreas and forming the base of the crater-like lesion. There was a slight polymorphonuclear cell response to the tissue necrosis. Two partially thrombosed veins and a normal large artery could be seen at the base of the ulcer (Fig. 2). Microscopy of the liver showed a massive zonal necrobiosis with gross fatty change, except in narrow zones round the central veins where liver cells survived. The portal areas were slightly enlarged and showed mild infiltration by inflammatory cells. There was no evidence of extra- or intra-lobular bile retention (Fig. 3).

Case 2. Shirley A., the twin of Case 1, was a breech delivery (birth weight 4 lb.). Feeding began on the fourth day and was difficult at first. There was slight jaundice on the fifth day and one feed was vomited, the vomit containing a little blood. Some abdominal distension was noticed during the second and third weeks and feeding continued to be difficult. The birth weight was not regained until the fifth week. There was a transient conjunctival infection (*Staph. aureus*), for which oral penicillin was given during the third week, but it cleared up rapidly. After regaining her birth weight progress was steady, and on discharge with her sister on January 11 1952, she weighed 6 lb. 10 oz. at the age of 10 weeks.

Progress and feeding at home were satisfactory and parallel with that of her sister. 'Neave's food' was added to the 'ostermilk' bottle feeds by the mother when the babies were 3 months old, and the feeds were taken well. Fretfulness, refusal of feeds and vomiting began at the same time as in the twin, on February 20, 1952. The baby was seen the next day by the family doctor and put on saline feeds for 24 hours, after which there seemed to be some improvement. There was no pyrexia. On again increasing feeds vomiting recurred and she was sent into hospital on February 24.

On examination she was pale and severely dehydrated. There was no jaundice. Stools were loose and watery and very frequent, and all fluid by mouth was vomited. The left ear drum was red and bulging but the rest of the respiratory tract seemed normal. Heart sounds were normal, and nothing abnormal could be felt in the abdomen. An intravenous drip of 1 in 5 normal saline with 5% glucose was set up and paracentesis performed on the left ear, and the baby was given penicillin and aureomycin, and her condition improved. However, blood appeared in the stools and vomit a few hours after admission, and within 24 hours both had the appearance of pure blood. Blood, 150 ml., was given when the baby appeared to be adequately rehydrated. Soon after admission a high-pitched and quite abnormal cry was noticed and lumbar puncture was performed; the fluid was normal in all respects. Stools and rectal swabs grew no pathogens. Four days after admission she had made some improvement and oral feeding was started again. The cry was still high-pitched and there were some abnormal limb movements. Feeding was slowly increased and the child improved steadily during the next week in which the stools returned to normal and there was only occasional slight vomiting. In view of the findings in the twin it was thought justifiable to attempt an x-ray investigation and some thin barium was given. This seemed to show some pylorospasm but no ulcer crater, and the child was put on 'eumydrin' before feeds. The following day the cry again became shrill and quite abnormal; there were neck stiffness, nystagmus, and twitching limb movements, and vomiting again began. She collapsed and died suddenly during the afternoon.

FIG. 4.—Photograph of ulcer in Shirley A.

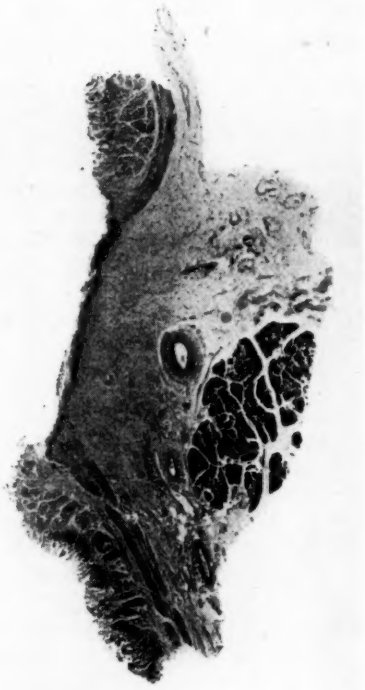

FIG. 5.—Section of ulcer in Shirley A. ×7.

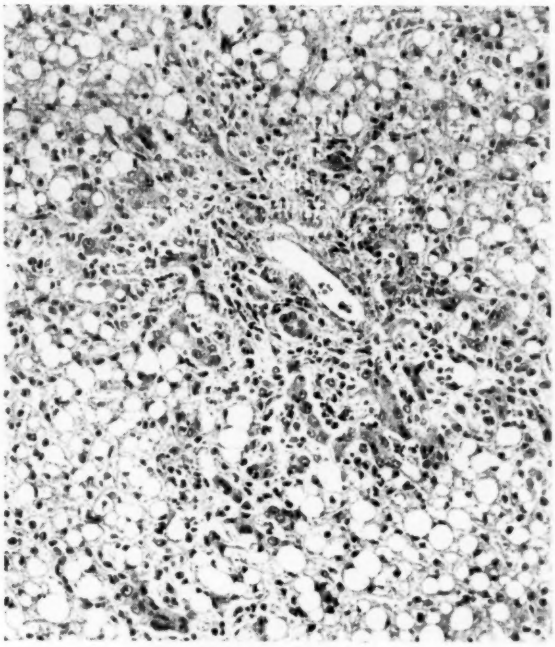

FIG. 6.—Section of liver in Shirley A. ×140.

At necropsy a duodenal ulcer was found in the same position as in the twin (Fig. 4). It was of irregular shape and punched-out appearance and measured 1·3 by 1·2 cm. in its maximum diameters. The base was formed by bile-stained necrotic debris. Microscopy showed a subacute ulcer penetrating the mucous and muscular coats, with evidence of some healing; between the necrotic base and the pancreas there was a fairly deep layer of granulation tissue with considerable fibroblastic activity and numerous new capillaries. No changes were seen in the larger arteries or veins (Fig. 5). The liver was a pale yellow. Sections of the liver showed diffuse cellular necrobiosis with gross fatty change. The portal areas displayed mononuclear cell and fibroblastic infiltration, and there was some early perilobular fibrosis, thin connective tissue strands linking adjacent portal areas (Fig. 6). There was slightly more reparative change in this liver than in that of the twin. Sections from the cerebral cortex, cerebellum, thalamus, hypothalamic region, lenticular nucleus, pons and medulla showed only some hyperaemia. The pituitary, adrenals, pancreas and spleen were normal to naked-eye inspection and on section. The kidneys on section showed congestion and mild fatty change in some cortical and medullary tubules, and slight calcium deposition in a few cortical tubules. The bronchi were normal. Sections from the lungs showed hyperaemia and focal collapse but no inflammatory changes. The stomach, jejunum, ileum and large intestines showed nothing significant to naked-eye or on microscopical examination.

Discussion

These 4-month-old twins died following an illness with diarrhoea and vomiting of obscure aetiology. Both had large duodenal ulcers and extensive liver damage. Jean died on the sixth day of illness and showed more acute changes and little evidence of the reparative processes seen both in the ulcer and in the liver of Shirley who survived for 12 days. There was nothing in the history or on subsequent enquiry to suggest any chemical poisoning, so that it is presumed that the intoxication was of infective origin.

The twins were binovular (appearance was dissimilar and there were two placentas) but the illness seems to have been identical and provided the unusual opportunity of observing in some detail what was essentially the same pathological process at two stages in its evolution. This has seemed to us to justify the placing on record of these cases.

It is of interest that in the experimental cincophen ulcer in dogs (Ivy, Grössman and Bachrach, 1950), liver changes occur—vacuolization and necrosis of the hepatic cells—which are strikingly similar to those in these babies. The mechanism which produces a cincophen ulcer is not completely understood. It is thought, however, that cincophen affects the detoxifying mechanism of the liver, particularly glucuronic acid conjugation. The depletion of glucuronic acid, which is an essential part of mucin, could lead to the formation of an ulcer. The formation of the cincophen ulcer can be prevented or retarded by the application of mucin, pectin or liver extract.

It is tentatively suggested that a similar mechanism may have been at work in producing the striking association of liver damage and duodenal ulceration in these twins with severe 'gastro-enteritis'. It is thought that in such cases treatment with mucin or pectin might be beneficial. In fatal cases, however, a careful search for the presence of erosions or ulcers in the gastro-intestinal tract should be made.

It is a pleasure to express our thanks and indebtedness to Dr. J. Mills, pathologist to the Royal Berkshire Hospital, in whose department the necropsies were carried out and to Dr. E. F. Chapman of Crowthorne, Berkshire, the family doctor.

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POISONING BY THE VOLATILE OILS IN CHILDHOOD

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The volatile oils play an important part in accidental poisoning in childhood, as can be seen from the figures quoted in a recent review (Craig and Fraser, 1953). The purpose of the present paper is to draw attention to the dangers of this form of poisoning, on which the recent literature is scanty, to suggest measures for its treatment and control, and to consider any points which may be applicable to the wider field of poisoning as a whole.

Craig and Fraser showed that, of 502 cases of accidental poisoning in childhood which had occurred in Edinburgh and Aberdeen between 1931 and 1951, the common toxic agents were volatile oils in 74 cases, household disinfectants in 39, barbiturates in 36, kerosene in 31 and iron in 24. The group of acids and alkalies caused only 11 cases. Of 454 deaths from accidental poisoning in childhood which had occurred in Britain during a similar period, 54 were caused by the volatile oils, the next commonest being strychnine in 41, acids and alkalies in 39, iron in 31 and disinfectants in 28. Only 10 deaths were due to barbiturate poisoning. That the volatile oils should top both the morbidity and mortality figures is surprising, considering the relatively slight attention which has been paid to this group.

The 74 cases seen in hospital were made up of camphor 29, turpentine 25, sassafras 5, eucalyptus 4, methyl salicylate (oil of wintergreen) 3, others 8. The 54 deaths were due to methyl salicylate 36, camphor 12, turpentine 2, eucalyptus 1, others 3.

Material

The present paper is based on the 74 cases of poisoning mentioned above. In 24 of these the records are either missing or so exiguous that analysis is unwarranted. The remaining 50 cases are otherwise unselected. Many of them are mild, but even these can contribute information on such points as the mode of ingestion and the first aid that was carried out.

Camphor

Camphor is a crystalline ketonic substance, closely related to the terpenes, which is obtained by distillation from cinnamomum camphorae. As a by-product of this distillation, essential oil of camphor (ol. camph. rect.) is also obtained. The main constituent of this oil is cineole (35%), with safrole, camphor, phellandrene, pinene, etc. Camphorated oil, on the other hand, is pure camphor (20%) in a vegetable oil (arachis oil). It is thus not strictly a volatile oil, but is sufficiently closely related to be treated clinically as such. Spirits of camphor contain 10% of camphor.

The toxic effects of camphor are mentioned in pharmacological works of reference, but little material is given which particularly applies to the problem in childhood. Single cases in adults have been described by Haft (1925) and Klingensmith (1934). A case in a mentally defective boy of 10 years was described by Cottrell (1931). Benz (1919) briefly described the chaos which reigned in a children's dormitory after all the occupants had been dosed with camphorated oil instead of castor oil, but unfortunately this graphic report is not susceptible of scientific analysis. Single cases in childhood have been reported by Davies (1887), Barker (1910), Haas (1916), Clark (1924), Blair (1929) and others. In a general survey of poisoning, Rubin, Recinos, Washington and Koppanyi (1949) include some discussion of 14 cases of camphor poisoning and 11 of turpentine poisoning.

Case records are available in 19 patients with camphor poisoning, all of whom took camphorated oil, and these are summarized in Table 1.

Two cases are reported in detail:

CASE 2. A boy of 5 years was given one teaspoonful of camphorated oil instead of olive oil for a cold. This happened about 7.45 a.m. He complained of the nasty taste and the mother discovered her error, but did nothing about it. However, the boy took a good breakfast and went to school. Shortly after 9 a.m. he vomited and began

TABLE 1
POISONING BY CAMPHORATED OIL

Case No.	Age (years and months)	Amount Taken	If in Error, Given for	Vomiting	Emesis	Gastric Lavage	Pallor or Collapse	Convulsion	Stupor	Coma	Muscular Excitability	Ataxia	Mental Changes	Cyanosis
1	1 yr. 5	dr. 1	Castor oil	30†	—*	+	—	25	+	—	—	—	—	—
2	5 yr. 5	dr. 1	Olive oil	90	—	—	—	—	+	—	+	+	+	+
3	9	<oz. ½	Castor oil	—	—	45	—	—	—	—	—	—	—	—
4	2	?	'In error'	—	—	+	—	—	—	—	—	—	—	—
5	1 yr. 4	dr. ¾	Glycerine	—	—	15	—	—	—	—	—	—	—	—
6	4½ yr.	oz. 1	Olive oil	10	6	+	—	4	+	—	+	+	+	—
7	1 yr. 11	?		70	—	100	65	60	—	—	—	—	—	—
8	2 yr.	dr. 2		5	—	+	—	—	—	—	—	—	—	—
9	1 yr. 8	?		—	—	—	—	+	—	—	—	—	—	—
10	1 yr. 1	?		—	—	+	—	—	—	—	—	—	—	—
11	2 yr. 11	dr. 1	Castor oil	5	—	50	—	—	—	—	—	—	—	—
12	2	?	Olive oil	—	—	—	—	—	—	—	—	—	—	—
13	2½ yr.	?		125	—	—	+	120	—	—	+	—	—	+
14	2 yr.	oz. ½		45	—	180	+	125	—	—	—	—	—	—
15	1 yr. 2	dr. 1	'Cough mixture'	—	—	60	—	?	—	—	—	—	—	+
16	1 yr. 4	dr. 1		35	32	—	+	30	—	—	+	—	—	—
17	1 yr. 4	dr. 1	'By mistake'	+	—	+	—	—	—	—	+	—	+	—
18	1 yr. 3	dr. 1	Cod liver oil	5	—	90	—	60	—	?+	+	—	—	—
19	2 yr.	dr. 2		45	—	—	+	120	+	—	—	—	+	—

* In the tables, — sign means only that the symptom was not mentioned in the case records. The dosages quoted are for the most part parental estimates, and in only a few cases should they be taken at their face value.

† Where numbers are quoted instead of + signs in the tables, they indicate the approximate time in minutes after ingestion at which a symptom appeared. Although some of these estimates must be inaccurate, they are correct in so far as they establish the sequence of events.

to stagger about the classroom. His legs seemed to be twitching. He did not talk, and seemed sleepy, though conscious. On admission, he was slightly cyanosed. He was confused but obeyed simple commands. He vomited again. No specific therapy was given and he was completely well within 24 hours.

CASE 6. At 8.40 a.m. a boy of 4 years was given one ounce of camphorated oil in mistake for olive oil. Four minutes later, he went into a generalized convulsion which lasted for two minutes. He then seemed comatose, but his mother induced vomiting by putting her finger down his throat, and he became brighter thereafter. He had a further two vomits before admission at 9.15 a.m. On admission, he seemed bright and interested, but his hands were jerking. Gastric lavage gave a return smelling strongly of camphorated oil. If left alone, the boy remained quiet, but he became very excited when disturbed. He was completely well within 24 hours.

It will be seen that in 11 of the 19 cases the camphor was administered by the parents. This proportion does not appear with any other toxic agent, and why it should happen with camphor, which has such a distinctive smell, is difficult to understand. If the cases in which the drug was given by the parents are excluded, the age incidence of camphor poisoning corresponds with that for poisoning as a whole.

Five patients in the present series developed no symptoms. It is of interest to note that four of these (Cases 3, 4, 10, and 12) were the youngest patients in the series. This raises the possibility that the youngest children splutter out most of what they are given because of the offensive taste, which in turn raises the whole question of taste in relation to accidental poisoning, a matter which will be dealt with at greater length later. Death has, however, been recorded in the youngest age-group.

Symptoms. There are four cardinal signs in camphor poisoning. These are:—

(1) INCREASED MUSCULAR EXCITABILITY. Case 2 affords a good example of abnormal muscular activity occurring without a convulsion supervening, but for the most part a case which shows muscle jerking will also show convulsions. These movements may herald a convulsion, or may follow a convulsion and gradually die away without a further convulsion occurring. They interfere with voluntary activity.

(2) CONVULSIONS. Although it is an established fact that convulsions occur in camphor poisoning, it does not seem to be generally realized how common these convulsions are. It will be seen that nine (or possibly 10) patients of the present series had one convulsion or more.

Rubin *et al.* report convulsions in five of their 14 cases. A convulsion may be the first sign of poisoning, or it may occur after other symptoms have appeared. Camphor convulsions do not carry the serious prognosis of strychnine convulsions, as all of the patients who convulsed subsequently recovered. A large dose may be expected to produce a prompt convulsion (Case 6).

(3) VOMITING. This may be the only symptom, or it may precede or follow other symptoms. It may occur within five minutes of ingestion, or may be delayed for as much as 90 minutes. There is evidence

that delayed vomiting leads to serious symptoms, as, of the seven patients who did not vomit for 30 minutes or more after ingestion, six developed convulsions and the seventh showed marked jactitations (Case 2). It is obvious, however, that a patient who has not vomited may not produce any symptom. But if vomiting has occurred before the patient has been seen, and the vomiting has been delayed, then the case must be regarded as potentially serious.

(4) MENTAL CHANGES. These are difficult to assess in children, but terror (Klingensmith) and maniacal behaviour (Haft) have been recorded. Confusion and irritability are common.

Pallor or cyanosis and collapse may occur, but seem usually to be secondary to other symptoms. Death from camphor poisoning is said to occur commonly from respiratory failure. This may follow a series of convulsions (Barker) or may occur early (Blair). In Blair's case, respiratory failure occurred within 45 minutes of ingestion and the child was kept alive by artificial respiration for 30 minutes before spontaneous respiration was resumed, accompanied by tonic muscular contractions. On the other hand, death has apparently occurred in status epilepticus (Clark, Davies). The situation is paralleled in experimental work. The rats used by Grove (1910) died in respiratory failure, the guinea-pigs used by Carnot and Cairis (1914) in the prostration produced by status epilepticus. It appears that children may react in either way, which has to be considered in treatment. From the present series, respiratory failure seems to be rare, but this may only mean that the series is composed of mild cases.

Sequelae seem to be rare. The mentally defective boy described by Cottrell had marked meningitic signs for four days. Klingensmith's case was readmitted on the fourth day because of severe headache. All the cases in the present series appeared to recover rapidly, and none was readmitted.

Treatment. It is startling to observe that artificial emesis was induced by the parent in only two of the 19 cases, and in these two only after a convulsion had occurred. The need for speedy emesis was underlined above, when it was pointed out that the more severe symptoms appear regularly in those cases in which vomiting has been delayed. A practitioner who has been 'phoned about a case of poisoning cannot assume that a parent will carry out the 'obvious' measure of stimulating vomiting.

Gastric lavage is also indicated, whether vomiting has occurred or not. Lavage in a patient liable to have a convulsion is not always a wise practice, but camphor, being in liquid form, is relatively easily removed from the stomach, and much may be gained from a successful lavage.

Many cases need otherwise only be treated on expectant lines. However, convulsions cannot be taken lightly. It is true that a convulsion is not a particularly grave prognostic sign, yet convulsions occurring with increasing frequency are ominous (Carnot and Cairis). On the other hand, sedation must be undertaken with care, because of the risk of eventual respiratory failure. Barker found chloral ineffective, but only gave one small dose. He was also unable to make full use of chloroform, as the patient's breathing deteriorated, cyanosis became marked, and the fits, though less frequent, were more severe. In a severely poisoned child any anaesthetic may act as a respiratory depressant except when given by the most skilled hands. The short-acting barbiturates, given intravenously, or paraldehyde given intramuscularly, seem to be the most rational form of treatment.

Toxicity. One drachm of camphorated oil has caused the death of a child of 16 months, and the same dose caused marked symptoms in a boy of 6, quoted in the present series. A convulsion occurred four minutes after a boy of 4 had taken one ounce, and this child must be considered fortunate because his mother at once induced vomiting, which was quickly followed by further spontaneous vomiting. A review of the present series and of the available literature suggests that 1 drachm is a dangerous dose for a toddler, and 2 drachms for a school child.

Eucalyptus

Single cases of eucalyptus poisoning have been described by Wood (1900), Myott (1906), Benjamin (1906), Orr (1906), Allan (1910), Garrett (1925), Sewell (1925) and Gibbin (1927). Kirkness (1910) described two cases. It is an uncommon poison in childhood, but death has been recorded. The principal findings in three further cases are summarized in Table 2.

One case is reported in detail.

TABLE 2
POISONING BY EUCALYPTUS OIL

Case No.	Age (years and months)	Amount Taken	Vomiting	Emesis	Gastric Lavage	Respiratory Signs	Colour	Stupor	Shock	Vertigo	Ataxia	Myosis
1	3 yrs.	oz. 1	90	—	120	—	Flush	100	—	?	90	—
2	4 yrs.	?	—	15	60	—	Flush	—	—	10	10	—
3	7	dr. 1	—	—	30	++	Pale	5–10	+	—	—	+

CASE 3. A boy, aged 7 months, was given a teaspoonful of oil of eucalyptus at 8.15 a.m. He coughed and choked, and some of the oil was spilled. A few minutes later he became drowsy. When first seen, 25 minutes after ingestion, he was pale and collapsed, with rapid, shallow respirations, and a rapid and feeble pulse. The limbs were flaccid, the reflexes present but weak. The pupils were pin-point, with no reaction to light. Rhonchi were heard at both bases. The stomach was washed out, the return smelling strongly of eucalyptus. By 11 a.m. his breathing had improved, but there was considerable exudation in the respiratory tract, and the back of the throat required frequent swabbing. His temperature rose to 103·4° F. By 4 p.m. the child was showing spontaneous movement, and was beginning to cry. He had a stool smelling strongly of eucalyptus at 11 p.m. After 24 hours the respiratory tract was almost dry, the temperature normal, the general state good. The pupils were no longer pin-point, but were not reacting well to light. The odour of eucalyptus did not leave the breath until 72 hours after ingestion. He was discharged on the sixth hospital day.

Symptoms. There are three major manifestations of eucalyptus poisoning:

(1) A DEPRESSANT EFFECT. A toxic dose of eucalyptus usually leads to drowsiness in a few minutes, and the patient may be deeply unconscious in a quarter of an hour. Vertigo and ataxia were observed in two of our patients, neither of whom became shocked, and it seems that these symptoms are indicative of a relatively mild degree of poisoning, the more serious cases being quickly overcome by stupor. This is borne out by Gibbin's patient who stated that he had experienced epigastric pain, nausea, weakness in the legs, giddiness, cold sweats, rigors and headaches before becoming unconscious. A constricting type of abdominal pain seems common.

(2) RESPIRATORY SYMPTOMS. Although Case 3 of the present series resembled Gibbin's case in having shallow respirations, the majority show stertorous breathing. That the moisture in the respiratory tract is probably a direct effect of the eucalyptus is suggested by the work of Boyd and Pearson (1946), who showed experimentally on a number of mammals that eucalyptus or oil of turpentine instilled into the stomach significantly increased the output of respiratory tract fluid. They further showed that there was an optimal dose (about 50 mg. kg.) in producing this effect, and that a larger dose led to an actual fall in the effect. This may explain the variability of the appearance of respiratory symptoms in poisoned children.

(3) MYOSIS. Pin-point pupils have frequently been recorded in eucalyptus poisoning. This is of some importance, as the conjunction of pin-point pupils and stertorous breathing might suggest morphine poisoning, as has been pointed out by Wood, or poisoning by amidone or an organic phosphate. On the other hand, the pupils may be dilated and the breathing shallow (Kirkness). However, the smell of eucalyptus should make the diagnosis obvious.

Urinary symptoms have been reported.

Treatment. Emesis should be induced and gastric lavage carried out. As there is a central depression of respiration, it seems logical to use a stimulant such as nikethamide, although it should be used with care if the eucalyptus has been taken in liniment which also contains camphor.

Due attention should be paid to the respiratory tract, as Myott's patient died of respiratory complications, the lungs being grossly congested and friable at necropsy. Excess mucus should be removed from the respiratory passages, and oxygen given where necessary. Antibiotics should be given prophylactically.

Toxic Dose. The toxic dose of oil of eucalyptus is difficult to determine. An adult male died after taking 6 drachms (Myott), and the baby who has just been described was severely ill after taking less than one teaspoonful. However, one must remember that all the children brought to hospital with reputed eucalyptus poisoning developed symptoms, and the same applies to sassafras poisoning. This is not at all usual with other poisons, as many of the patients show no signs or symptoms of having actually taken the drug. The conclusion to be drawn is that even a few drops of eucalyptus or sassafras may be sufficient to cause symptoms. As symptoms may rarely take as long as two hours to appear (Case 1), it would seem advisable to keep all cases of reputed eucalyptus poisoning under observation for that time, unless gastric lavage has been carried out within a short time of ingestion without eucalyptus being detected in the washings.

Sassafras

Oil of sassafras is sometimes used against headlice, although its popularity is waning. It also exists in a synthetic form, which may be expected to have the same properties as the natural substance. Oil of sassafras is 80% safrol, with small amounts of pinene, phellandrene and camphor. Crude oil of camphor may be divided into a light fraction, from which medicinal camphor is prepared, and a heavy fraction with a high safrol content, from which synthetic oil of sassafras is derived. One of the patients in the present series (Case 4) ingested the synthetic form.

The literature on sassafras poisoning is scanty. The U.S. Dispensatory records the case of a young

man who ingested one teaspoonful of oil of sassafras, developed vomiting and collapse with dilated pupils, passed into stupor, and died (Cincinnati Lancet-Clinic, December, 1888). Five cases are now reported, the results being summarized in Table 3.

All five children took the oil themselves, so no reliance can be placed on the estimated amount taken. It is probable that all the figures are over-estimates.

Symptoms. The U.S. Dispensatory records that experimental work, indicating that sassafras kills by a central paralysis of respiration preceded by a greatly depressed circulation, has been done by Heffter (1894).

Symptoms first appear within 10 to 90 minutes of taking the oil. The clinical picture in many ways resembles that of eucalyptus poisoning, except that vomiting and signs of shock are more common in sassafras poisoning, while myosis and respiratory symptoms were not apparent in the five cases here discussed. All the patients vomited, all but one showed signs of shock, three of the five showed vertigo, two were stuporose and one was aphasic.

Treatment. The use of emetics is well exemplified in Case 2. The mother sought the help of the police as soon as the accident occurred, and the police gave repeated emetics until the vomitus no longer smelt of oil. This therapy, more energetic than is applied to the majority of poisoning cases before referral to hospital, may well have averted serious symptoms, as the child was stuporose within 10 minutes of ingestion. Once in hospital, the child responded dramatically to an injection of nikethamide.

Toxic Dose. As an adult male has died after taking one teaspoonful of oil of sassafras, it is probable that a few drops would be sufficient to kill a toddler. It seems remarkable that the Registrar General's returns for the last 20 years contain no record of a death from sassafras poisoning.

Turpentine

Oil of turpentine (spirits of turpentine) is composed largely of terpenes. Its main constituent is pinene, and from pinene there can be derived synthetic camphor. Rectified oil of camphor contains small quantities of safrol, pinene and phellandrene, all of which are also found in oil of sassafras. Such links are common throughout the volatile oil series, and are mentioned here to show why turpentine is best considered as a poison in its relation to the other volatile oils.

Recent reports of the toxic effects of oil of turpentine have largely referred to its use in industry and to its absorption through the skin. Single cases of ingestion have been described by Grapel (1901), Stanwell (1901) and Harbeson (1936). Sixteen further cases are summarized in Table 4.

TABLE 3
POISONING BY OIL OF SASSAFRAS

Case No.	Age (years and months)	Amount Taken	Vomiting	Emesis	Gastric Lavage	Pallor	Shock	Stupor	Vertigo	Aphasia
1	2 yr.	dr. ¾	60	—	120	—	—	—	—	—
2	1 yr. 2	dr. 2	15	5	+	15	+	10	—	—
3	1 yr. 9	oz. 2	<30	—	>60	<60	+	30	<60	—
4	2½ yr.	dr. 2	120	*F	140	120	120	—	90	90
5	1 yr. 3	dr. 2	65	—	120	60	+	—	65	—

* F = emesis attempted but failed.

TABLE 4
POISONED BY OIL OF TURPENTINE

Case No.	Age (years and months)	Quantity	Choking ± Respiratory Signs	Vomiting	Emesis	Gastric Lavage	Shock	Stupor	Convulsion	Ataxia	Urine	Pyrexia
*1	5	dr. 1	+	—	F†	60	—	+	—	—	—	—
2	1 yr. 7	<oz. 3	+	—	F	190	—	?90	—	—	R.B.C.s	+
3	1 yr. 9	oz. 2	+	5	3	—	—	60	—	—	Smell Few R.B.C.s	+
*4	2 yr.	oz. ½	—	10	—	—	—	—	—	—	—	—
5	2 yr.	?	—	—	—	30	—	—	—	—	—	—
6	2 yr. 10	?	—	+	—	+	+	—	—	—	—	—
7	1 yr. 2	oz. 4	—	—	F	430	—	240	550	240	—	+
8	1 yr. 1	oz. 1	+	5	3	20	—	+	—	—	—	—
*9	5 yr. 7	?	—	5	3	+	—	—	—	+	—	—
10	2 yr. 8	?	—	—	—	15	—	—	—	—	—	—
11	1 yr. 1	?	—	245	240	—	—	—	180	—	—	—
12	1 yr. 8	?	+	30	—	35	35	—	—	—	—	+
13	1 yr. 1	?	—	—	—	30	—	+	—	—	—	—
14	1 yr.	?	+	5	—	+	—	—	—	—	—	—
15	3 yr.	oz. 1	+	5	3	15	—	—	—	—	—	+
16	1 yr. 3	oz. 3	—	10	—	90	—	—	—	—	R.B.C.s	—

* Cases 1, 4, and 9 took 'turpentine substitute' which contains hydrocarbons derived from petroleum.

† F = emesis attempted but failed.

One case is described in detail.

CASE 7. A girl of 14 months was reputed to have drunk 4 ounces of turpentine. The mother attempted to induce vomiting by giving salt and water, but failed. The child then gradually 'became drunk'. She was sleepy, and would neither sit nor stand. The child also seemed 'jumpy, and likely to have a convulsion'. She was admitted to hospital six hours after ingestion,when her temperature was 101·6° F., pulse 140, respiration 50. The child was sleeping, but twitching markedly. Gastric lavage was done, and the result smelt strongly of turpentine. The pulse rose to 170, the respirations to 70, and the child then had a convulsion lasting for 15 minutes. She was stuporose and screaming for half-an-hour after the convulsion. She was well within 24 hours, and no sequelae appeared.

In view of the relative mildness of most cases of turpentine poisoning, Harbeson's case is also described. This was a child of 11 months who was given two teaspoonfuls of spirits of turpentine as an anthelmintic. She had a convulsion a few hours later and became comatose, with cyanosis, hyperpyrexia and marked tachypnoea and tachycardia. She died a few hours after the convulsion without having regained consciousness.

Symptoms. Turpentine produces a wide range of toxic effects. It is difficult to describe a 'classical case' of turpentine poisoning. Symptoms which may appear are:

(1) VOMITING. This occurred spontaneously in only four of the 16 cases.

(2) STUPOR. This appears to be the commonest of the more severe symptoms. It occurred in six patients, four of whom had not vomited spontaneously and five of whom had not had vomiting induced or gastric lavage before the symptom supervened.

(3) CONVULSIONS. These are not commonly described as signs of turpentine poisoning, yet a convulsion occurred in Harbeson's case and in two children in the present series. Both of the latter had previously had a febrile convulsion, and the inference seems to be that turpentine has a mild convulsant action which may cause a convulsion in a predisposed child, even in the absence of pyrexia. Convulsions do not seem to occur till some hours after ingestion.

(4) IRRITATION OF URINARY TRACT. It is well known that the urine smells of violets in turpentine poisoning (and also in eucalyptus poisoning). This sign was observed in only one of the 16 cases, and excess of red cells was observed in three only.

(5) RESPIRATORY SYMPTOMS. There was a history of choking at the time of ingestion in seven cases, and respiratory symptoms appeared in two.

Pyrexia, ataxia, shock, tachycardia, sweating and leucocytosis may also appear.

In their 11 cases, Rubin *et al.* found coma or drowsiness in six, fever in four, vomiting in four, and pneumonia in one, findings which correspond well with my own.

Treatment. Treatment in the first instance is by emesis and gastric lavage. Case 7 shows that it is almost true to say that 'it is never too late to wash out the stomach', as turpentine was found there six hours after ingestion.

The treatment of stupor which is liable to be punctuated by a spontaneous convulsion is something of a problem. However, convulsions do not seem to lead to death, whereas coma may, so that careful use of stimulants seems to be indicated. Other symptoms seem to be so uncertain in their appearance that treatment can only be symptomatic.

Toxicity. In Harbeson's case, 2 drachms caused the death of a 7-month-old baby. In only one case of the present series (Case 1) is the dose known with any accuracy, the parent having given turpentine instead of gripe water. One drachm was sufficient to cause stupor in a 5-month-old baby, which roughly coincides with Harbeson's case. One ounce produced very severe urinary symptoms in a woman of 20 years, the urine still smelling of violets 24 *days* after ingestion (Grapel). A woman of 46, who had her stomach washed out within 15 minutes of taking 10 ounces of turpentine in a suicide attempt, developed no symptoms (Stanwell). It is noteworthy that her breath did not smell of turpentine and that the lavage was undertaken initially as a means of diagnosis. This small clinical point deserves attention.

It seems likely that 1-2 drachms would be necessary to produce severe symptoms in a toddler, which presumably accounts for the mildness of turpentine poisoning relative to that of the other volatile oils.

Methyl Salicylate (Oil of Wintergreen)

Oil of wintergreen (ol. gaultheria, lin. meth. sal.) is almost unique among the volatile oils in that it is very nearly a pure substance, containing 98% methyl salicylate. Methyl salicylate is converted in the stomach to methyl alcohol, which is absorbed as such, and salicylic acid, which is absorbed after being converted to sodium salicylate in the intestine. The methyl alcohol is seldom produced in sufficient quantities to play much part in the picture of poisoning, the effect produced being that of salicylism, as 75% of the methyl salicylate is available as salicylate. A teaspoonful of oil of wintergreen will supply 45 grains of salicylate, obviously enough to endanger the life of a small child, particularly as

young children have a notoriously poor tolerance for salicylates. The symptoms produced by oil of wintergreen are thus quite different from those due to other volatile oils.

The literature on methyl salicylate poisoning is copious. Reviews have been published by Stevenson (1937), Macready (1943), and Mouren (1949), and the biochemistry of salicylate poisoning has been thoroughly investigated by Erganian, Forbes and Case (1947). Nevertheless, three further cases are now reported, as post-mortem examination was carried out in one, and as attention should be drawn to this extremely dangerous poison in the British literature.

In two of these three cases, no symptoms appeared. The children were aged 1½ and 6 years. Gastric lavage was carried out in one within 20 minutes of ingestion. In the other, the precise time of lavage is uncertain, but it was certainly less than one hour after ingestion. The gastric contents in both cases smelt strongly of oil of wintergreen. Both children were admitted to hospital, but remained perfectly well. The third case presents a striking contrast.

CASE REPORT. At 11 o'clock one morning, 34 hours before admission to hospital, a girl aged 25 months drank oil of wintergreen. The precise amount was unknown, but it was less than half an ounce. Castor oil was given. She remained well until five hours after ingestion, when she began to vomit and had two loose stools. She then became irritable and developed dyspnoea, but she had had a cold for two days and these signs were not considered serious. She was given a further dose of castor oil, but during the night she vomited repeatedly and had several loose motions. About 17 hours after ingestion, she was pale and dyspnoeic and did not recognize her mother. By the time she was admitted, she was flaccid and deeply unconscious. Her breathing was markedly acidotic, and she showed occasional muscle twitchings (temperature 100° F., pulse 160, respiration 40). There were no added signs to be heard in the chest although her own doctor had noted bronchitic signs before sending her in. An intravenous drip of glucose was set up, but the child died soon after, her temperature rising to 106° F. before her death, which occurred 36 hours after ingestion. No biochemical studies were made.

At necropsy Dr. Kenneth Rhaney found numerous submucous haemorrhages in the stomach.

The spleen was considerably enlarged, pale grey and soft, with very prominent Malpighian bodies. Microscopically, some of the Malpighian bodies showed necrosis and hyaline material in their centres. The pulp contained an excess of polymorph leucocytes.

There was oedema of the bases of the lungs.

The liver was slightly enlarged, soft, pale orange-yellow with a mosaic of delicate brown lines, apparently the result of severe fatty change. Microscopically, there was a moderate degree of fatty change in all parts of the lobules, most severe in the peripheral zone. Many of the cells had pyknotic nuclei.

In the kidney there was moderately severe venous congestion. Microscopically, the cells of the convoluted tubules and the ascending limbs of Henle's loops showed widespread cloudy swelling, with narrowing or obliteration of the lumen. Many cells had separated one from another and some had been desquamated. Urine taken at necropsy gave a positive Gerhardt test and a negative Rothera test, and contained sheets of cells, but no casts.

The changes were consistent with chemical poisoning.

Symptoms. It is not intended to give here a detailed description of the signs of salicylism. On the other hand, it is desirable to stress the particular danger of wintergreen poisoning. The poison is a rare one, yet, over the last 20 years, it is second only to strychnine as a lethal poison in childhood.

There is usually vomiting shortly after ingestion, although this was absent in the case described above. There then ensues a period of several hours during which there may be no untoward signs (Stevens and Kaplan, 1945). There may be mild subjective symptoms during this period (Crossland, 1948), but not such as a toddler is likely to explain in words. After this delay, the signs of severe acidosis complicated by liver damage gradually appear, and the patient is likely to die unless energetic therapy is undertaken.

Dérobert and Gascoin (1950) described a child in whom the march of symptoms was more rapid. He was put to bed after his midday meal within reach of a bottle of oil of wintergreen, and at 2.30 was found pale and reeking of wintergreen. Copious vomiting was immediately induced, but by 4 p.m. he showed muscular jerking, respiratory embarrassment, cyanosis of the whole body, profuse sweating, cold extremities, a rapid pulse, projecting eyes and strabismus. He was sent at once to hospital, but died within 45 minutes of admission. There was no smell of wintergreen in the gastric washings, but there were large quantities in the urine at necropsy. Although it is impossible to work out a precise timetable for the early part of the history, it seems that this child probably took a very large quantity of wintergreen and, although all that was in the stomach was removed by emesis within an hour of ingestion, enough had passed into the intestine to cause rapid death. A similar case is described by Gaburro (1952).

Treatment. Emesis should be induced pending gastric lavage, in which sodium bicarbonate should not be used as it is said to increase the solubility of methyl salicylate (Aikman, 1949). At the first sign of acidosis intravenous therapy should be begun, glucose being given to counter the toxic effect of salicylate on the liver and M-6 sodium R-lactate to

counter the acidosis. Therapy can be controlled by studying the CO_2 combining power of the blood. Vitamins K and C should also be given. If pulmonary signs appear, antibiotics should be exhibited.

Methyl salicylate poisoning is a pitfall for the inexperienced resident medical officer. He should remember that a clear return from gastric lavage does not necessarily preclude severe toxic symptoms if the child has already vomited, or if the poison has been taken some time before. He must also remember that a child who has no abnormal signs four hours after ingesting wintergreen may be beyond medical aid a few hours later. All reputed cases of wintergreen poisoning must be admitted to hospital.

Other Volatile Oils

The volatile oils so far discussed include all those known to have caused deaths in Great Britain during the last 20 years, except for oil of citronella, which has been responsible for one fatality. Oil of chenopodium has caused six deaths in children in Padua in the last 10 years (Gaburro). There remain to be mentioned four cases in which the oils were taken in compound form.

CASE 1. A girl of 20 months took an unknown quantity of camphor and eucalyptus. She was admitted to hospital 90 minutes later, showing pallor, stupor and collapse, but made a good recovery. This cannot be taken to indicate that camphor and eucalyptus together invariably combine to produce a depressant effect, as the relative amounts of the two oils taken in this case were unknown.

CASE 2. A girl of 35 months swallowed some 'three oils', vomited twice in the next half hour, and immediately thereafter began to have a series of short convulsions. She then became comatose, and remained drowsy the next day, but was well in 48 hours. 'Three Oils' has no fixed formula, and the oils may be chosen from arachis, olive, cajuput, eucalyptus, camphor, lavender, turpentine, amber, red oil, etc. In the present case the main constituent seems to have been camphor, but possibly a depressant oil, even eucalyptus, was also present.

CASE 3. A boy who swallowed 'chilblain liniment' had his stomach washed out within 15 minutes and developed no symptoms.

CASE 4. A boy of 2½ years swallowed an unknown amount of linimentum A.B.C. When admitted, he was pale, twitching and delirious, with widely dilated pupils which did not react to light. He recovered.

This case has been included with the liniments only as a warning, as the symptoms are primarily those of aconite poisoning. One teaspoonful of linimentum A.B.C. contains approximately 1/60 gr. of aconite (toxic dose for an adult, 1/300 gr.), and gr. 1/16 belladonna alkaloids, in addition to camphor and chloroform. The extreme toxicity of this preparation is obvious.

Discussion

The volatile oils are not chemically pure substances. Broadly speaking, they contain alcohols, esters, aldehydes, ketones, phenols, ethers, hydrocarbons usually in the form of terpenes, and nitrogen or sulphur compounds; certain solid oxygenated principles are called camphors. One chemical substance may be present in several of the oils. Consequently, it is not surprising to find that there is considerable overlapping in the toxic symptoms of the oils.

Camphor causes nervous excitability and convulsions. Turpentine occasionally causes convulsions, but usually causes depression with occasional respiratory symptoms. Eucalyptus causes a depression of rapid appearance, respiratory symptoms often being severe. Sassafras causes ataxia, pallor and shock, with some depression. Separate from the others in the group is oil of wintergreen, which gives symptoms of salicylate poisoning.

The present survey frequently emphasizes the need for prompt emesis and gastric lavage in treating poisoning cases, and it may have been felt that too great stress has been laid on what is obvious. However, one has only to consider the records of these 50 children to realize how seldom emesis is induced or gastric lavage carried out as first-aid measures. Gastric lavage is often difficult in toddlers, and its omission by practitioners living close to hospital is understandable, but failure to induce emesis in so many cases is surprising. It is of interest that emesis was carried out more often in turpentine poisoning than in the other forms, which suggests that the general public may believe that poisoning by 'household' poisons is more serious than poisoning by medicines or medicinal applications. This would be a dangerous opinion to hold.

It has been pointed out that five of the cases of camphor poisoning discussed showed no symptoms, and that four of these were the youngest patients in the series, which raised the possibility that the youngest patients recognize and reject an offensive taste. Another consideration is that convulsions occurred in only three of the eight patients over the age of 13 months who were given camphor in error, whereas convulsions occurred in six of the seven patients over the age of 13 months who took the camphor themselves. Can it be concluded from this that a bad taste is no great deterrent to a normal toddler who is investigating a new substance or does it mean that children who poison themselves tend to have abnormalities of oral sensation? The evidence is insufficient to sustain any conclusion, but the point might become one of considerable importance in devising means of cutting down accidental poison-

ing in childhood, so that further investigation seems desirable.

The prevention of poisoning by the volatile oils involves two considerations; how to stop parents giving their children camphor by mistake, and how to stop children ingesting volatile oils.

The first half of the problem almost defies solution. If a mother cannot recognize a poison bottle, a label 'Not to be taken internally', and the strong and characteristic smell of camphor, what *will* she recognize? A distinctive colouring? Such a suggestion might be worth a trial, but it is doubtful if it would be effective.

The great danger of the volatile oils to children lies in their extreme toxicity, and the problem is not to make the oils unpalatable or difficult of access, but to keep them away from children altogether. It is necessary to educate the public, and it seems that the best way to educate the public in the present instance is to give it a little trouble. Some curb should be put on these oils, which can all be sold across the counter of a chemist's shop. It seems desirable to remove such highly dangerous substances as oil of wintergreen and linimentum A.B.C. from the pharmacopeia, and substitute similar ointments, as ointments appear to be very rarely ingested by children. The other oils, except for oil of turpentine which has relatively mild toxic effects, should either be obtainable only on a doctor's prescription, or else the buyer should have to sign a 'poison book' to draw his attention to the danger of what he is buying. It is also necessary for the doctor to be aware of the dangers of the volatile oils before prescribing them in a household which contains children, and for a chemist to stress the danger when selling them.

Summary

It is pointed out that the volatile oils as a group head the morbidity and mortality lists for accidental poisoning in childhood. Camphorated oil and oil of turpentine are the oils most commonly ingested, but oil of wintergreen accounts for three times as many deaths as camphor, the second commonest lethal agent. The symptoms and treatment of poisoning by camphor, eucalyptus, sassafras, turpentine and oil of wintergreen are discussed. It is suggested that the sale of these dangerous poisons, with the exception of turpentine, be controlled.

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BORIC ACID POISONING IN INFANCY ARISING FROM THE TREATMENT OF NAPKIN RASH

BY

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Accidental poisoning is not always recognized. If there is no leading history of the ingestion or exposure to poison the signs can easily be misinterpreted. In this way boric acid poisoning of infants may remain unsuspected, especially when it occurs by absorption through the skin.

Boric acid has been in clinical use as an antiseptic for 80 years. Soon after its introduction for this purpose by Lister reports of fatal poisoning began to appear (Molodenkow, 1881). Many deaths have been recorded following its ingestion, parenteral injection, irrigation or packing of wounds and body cavities, or application to damaged skin. In spite of these, the drug has continued to be regarded as bland and harmless.

Its local use in ammoniacal dermatitis of infants was first advised by Cooke (1921) when he demonstrated that the rash was due to bacterial decomposition of urine. However, it is only recently that poisoning by boric acid has been attributed to its employment in this way. Fellows, Campbell and Wadsworth (1948) reported the deaths of two young infants after napkin rashes had been treated with boric acid; they considered fatal poisoning proven in one case and suspected it in the other. Single fatal cases have been discussed by Abramson (1949), Brooke and Boggs (1951) and Bumbalo (1952), while Fisher (1951) has briefly recorded eight other deaths. Whether boric acid can be absorbed through the intact skin of the healthy adult is still disputed, but dangerous amounts can unquestionably penetrate the infant's skin when it is reddened and excoriated. In the belief that poisoning by this route may be commoner than has been realized, an example is reported. It was not fatal.

Case Report

A boy aged 4 weeks, the first child of intelligent parents, was admitted to the Royal Hospital for Sick Children, Edinburgh, in March, 1952.

He was healthy at birth, weighing 6½ lb. (2·95 kg.) after a normal delivery. Breast-milk failed in the second week and was replaced by half-cream dried milk. The child remained well until five days before his admission to hospital when the buttocks became slightly sore. Zinc and castor oil ointment was applied and powdered boric acid was sprinkled on all napkins. The mother had already been rinsing the napkins in boric solution as a routine precaution. The rash did not improve but the baby was otherwise well until two days before admission when he began to vomit. Feeding was then restricted to sugar and water, which was largely retained. Mild diarrhoea developed on the day of admission, with small, dark-green motions. For this reason, and because the state of the buttocks had become much worse, he was sent to hospital.

The child weighed 7¼ lb. (3·3 kg.) on admission and, although irritable, was in a satisfactory general condition. There was severe and widespread excoriation of the buttocks, perineum and thighs, and of the greatly swollen scrotum. A grey eschar extended along each side of the natal cleft, and the inguinal glands were enlarged. There was intense erythema of the tips of fingers, thumbs and toes, as well as of the nose and the lobes of the ears. There was a slight macular rash on the face but no rash on the rest of the body. The mouth and throat were dry, but there was no other evidence of dehydration. The ear drums were normal. Abdominal examination was negative, with the spleen not palpable and the liver edge felt ¼ in. (0·6 cm.) below the costal margin. A few scattered rhonchi were heard in the chest, but no abnormality was detected in the heart. Apart from the general irritability, the central nervous system was normal.

Examination of the urine showed a *p*H of 5·0, and a trace of albumin but no sugar; microscopically, only urates were seen. Both the flame test and the turmeric paper test for borates were strongly positive. Culture of rectal swabs on three successive days showed no pathogenic organisms of the salmonella or dysentery groups. *Staph. aureus* and pneumococci were grown from a throat swab. Haematological findings were: Hb, 84% (Sahli), red blood cells, 4·1 m., leucocytes, 3,900, and platelets 120,000 per c.mm. A blood film was normal, the bleeding time was 2½ minutes and the clotting time (capillary method) 4½ minutes. The following biochemical estimations were made 12 hours after admission: serum CO_2- combining power 56 vol. %, serum chloride 620 mg., serum sodium 354 mg. and urea nitrogen 18·5 mg.

per 100 ml., thymol turbidity test 1 unit, cephalin cholesterol flocculation reaction 0. The Wassermann reaction had been negative on routine examination of the mother during pregnancy, and also in a specimen of cord blood taken at birth.

The buttocks were swabbed with saline solution and exposed to the air. After gastric lavage, which yielded clear washings, oral feeds of a glucose and saline mixture were started, with chloramphenicol, 100 mg. four-hourly. Twelve hours after arrival the child's condition suddenly deteriorated. He vomited altered blood and mucus and appeared shocked, with sighing respirations and cold extremities. Vitamin K, 10 mg., was given intramuscularly and it was decided to stop feeds by mouth and to set up an intravenous drip of half-strength Ringer-lactate solution with 5% glucose. During this procedure there was a short generalized convulsion. No further vomiting occurred, but eight small loose stools were passed during the first 24 hours in hospital. On the day after admission the tests for borates in the urine were still strongly positive.

The child's condition thereafter was good, in spite of two more convulsions. The erythema subsided and the lips began to peel. The faecal benzidine reaction was weakly positive, but the urine ceased to contain albumin. The intravenous drip was stopped after two days, 21 fluid ounces (596 ml.) having been given, and milk feeds were substituted. Apart from the convulsions, no abnormal signs were found at any stage on clinical examination of the central nervous system. The liver function tests, repeated after four days, gave the same results, and the size of the liver was unaltered.

Fever was absent until 12 days after admission when there was a brief rise in temperature and the child again appeared ill. This fresh episode coincided with the development of a large pustule on the buttocks and with a recurrence of loose stools. Because the infant had been admitted to a gastro-enteritis ward, rectal swabs had been examined daily for *Bact. coli* of strains 0111 B4 and 055 B5. They had been negative so far, but the alpha strain (0111 B4) now appeared, probably as a result of cross-infection, and persisted for more than a month. Intravenous fluid therapy was not again necessary, but it was only after two courses of chloramphenicol and one of aureomycin that the mild diarrhoea ceased and the patient's condition became entirely satisfactory. His discharge from hospital was thus delayed until the forty-ninth day, although the buttocks had healed within a month. Rectal swabs had been negative for the last seven days. The weight on discharge was 8½ lb. (3·86 kg.).

Clinical Features

The signs of acute boric intoxication in infants are the same whatever the mode of entry of the poison. The present example illustrates the recognized sequence of events. The first signs are vomiting and diarrhoea, followed by dehydration and collapse, by skin eruptions, and in severe cases by repeated convulsions. The vomiting and diarrhoea are almost always present, but are often not severe, even when the poison has been ingested. Dehydration is usually moderate or severe, and is probably produced by the gastro-intestinal upset. However, Caujolle (1951) stated that there is an early and severe diuresis, and this may be a contributory factor.

Fever is a variable feature. It is often absent, and seldom exceeds 101° F. (38·4° C.) unless there are convulsions. There is sometimes haemorrhage in the form of haematemesis and melaena. These are usually mild, although the anaemia which developed in Bumbalo's (1952) case may perhaps have been due to intestinal bleeding. Haemorrhagic enteritis has often been found at necropsy and it is curious that this has been just as obvious in cases in which poisoning has occurred by skin absorption as in those poisoned by ingestion. We have found no report of haematuria, although slight albuminuria is usual.

A toxic rash is hardly ever absent and is, therefore, a valuable diagnostic sign. Occasionally it is minimal, and it might then be easy to attribute the illness to infective gastro-enteritis. The rash may take one or more of three forms: a widespread eruption, congestion of the digits, and aggravation of the napkin rash. The generalized rash is most often erythematous, but sometimes consists of red macules or scattered pustules. It is commonest on the face and chest, but may involve the whole of the head, body and limbs in an intense scarlatiniform eruption. This 'boiled lobster' appearance is quickly followed by desquamation. A peculiar feature is the occurrence of intense localized erythema of the tips of some of the fingers and toes. This may also affect the nose and ears. It is not always present, but may sometimes provide a clue to the diagnosis. The peripheral congestion may be limited to the nail-beds, which in some cases are described as bright pink or cyanotic. The damage to the buttocks need not be severe before toxic amounts of the drug can be absorbed, but when poisoning occurs by this route, progressive excoriation follows.

The infant is at first lethargic, but soon becomes irritable and hypertonic. In most fatal cases there have been severe and repeated convulsions, opisthotonos and terminal coma. Death usually occurs within six days, but may be delayed for two or three weeks, and is often associated with bronchopneumonia. The clinical manifestations in some of the principal reports are set out in Table 1.

Certain points, which may have a bearing on treatment, should be studied in any future case. The volume of urine should be measured, if possible, and the reason for the haemorrhage should be investigated. We found that the bleeding and clotting times

TABLE 1
CLINICAL SIGNS OF BORIC ACID POISONING OF INFANTS

Author	Age at Onset	Mode of Poisoning	Fever	Dehydration	Diarrhoea and Vomiting	Bleeding	Nervous Effects	Secondary Rash	Result
Abramson	Less than 7 days	Napkin rash, powder and ointment	?	Acutely ill and dehydrated	Both present	?	?	Bullous, shoulders	Died
Brooke and Boggs	9 months	Napkin rash, powder	High fever	Severe	Repeated vomiting, no diarrhoea recorded	Haematemesis and melaena	Coma and convulsions	Macular, confluent and widespread, nail-beds pink	Died
Bumbalo	12 days	Napkin rash, powder	Not above 99° F.	Moderate	Both present	Streaks of blood in stools. Became anaemic	Status epilepticus	Intense, widespread erythema	Died
Fellows *et al.*, Case 3	Less than 2 weeks	Napkin rash, ointment	101° F. on admission	?	Repeated vomiting, faeces not mentioned	?	?	Erythema of face and trunk, with scattered pustules	Died
Present case	3½ weeks	Napkin rash, powder	None	Mild	Both present	Haematemesis, occult blood in stools	Irritable, 3 convulsions	Macular rash on face, intense erythema of digits	Recovered
Watson	4½ months	Eczema, soaks and ointment	102° F.	?	?	?	Repeated convulsions, coma	Intense general erythema	Died
Barnum and Opper	Less than 7 days	Hospital feeding accident	Very slight	Severe	Both present	?	Severe meningismus	Widespread, erythematous or macular	20 Affected 5 Died
Grant and Wegner	10 days	Feeding accident	99 to 101·4° F.	Moderate	Vomiting. Severe diarrhoea.	?	Convulsions, opisthotonus	Mild general erythema	Died
Young, Smith and MacIntosh	6 to 11 days	Hospital feeding accident	99° F.	?	Both present	Haemorrhagic conjunctivae in 1 infant	Convulsions	Scattered areas of erythema and excoriation	8 Affected 6 Died

were normal, but the available evidence on coagulation and capillary fragility is inadequate. Brooke and Boggs (1951) recommended that liver function should also be assessed and the two tests employed in our case gave normal results. Finally, it would be interesting to know whether, after absorption through the skin, any significant quantity of boron is to be found in the faeces.

Methods of Diagnosis

The clinical signs resemble those of infective gastro-enteritis. Suspicion of poisoning would be aroused by a rash on the face and body, by haematemesis and melaena, and particularly by the presence of an antecedent napkin rash. Convulsions are not likely to be a prominent feature until the infant is already dangerously ill, but it is unusual for severe or repeated fits to occur in gastro-enteritis. Some cases may simulate congenital syphilis or bacillary dysentery, and these possibilities must be investigated.

If poisoning is suspected it may be confirmed by chemical examination of the urine or cerebrospinal fluid. Boric acid is excreted unchanged from the body, mainly in the urine. Of many possible methods, the carmine and turmeric paper tests appear to be the most convenient for hospital use. They are equally useful for the detection of borax.

Carmine Test. A few drops of the reagent, an 0·05% solution of carmine in concentrated sulphuric acid, are placed on a white tile. The urine is added drop by drop. A colour change from red to blue occurs if boron is present (Sorking, 1937). Normal urine should be tested simultaneously for comparison.

Turmeric Paper Test. The specimen is acidified with dilute hydrochloric acid. A strip of turmeric paper is soaked in it and the paper allowed to dry in the air. The presence of boric acid or borax is indicated by a red, which is changed to dark blue-green by dilute caustic soda or ammonia, but is restored by acid.

The development of the turmeric red is said to be hindered by phosphates, chlorates, nitrates and other substances. It is doubtful whether this is important under clinical conditions. We are unaware of any substance which interferes with the little-known carmine test, but recommend that both methods should be employed. A positive reaction with either test does not necessarily prove the existence of poisoning, since faint colour changes can be produced by non-toxic concentrations of the drug in the urine.

The diagnosis has sometimes been made only at post-mortem examination. The main reported findings have been exfoliative dermatitis, inflamma-

tion of the alimentary tract and haemorrhagic cystitis. Toxic degenerative changes in the liver and kidneys have been found, but are very variable in their intensity. The gastro-intestinal signs are usually most obvious in the ileum, where congestion, haemorrhage and ulceration are found. The lungs often show congestion, oedema or patchy bronchopneumonia. The brain may be congested or occasionally oedematous. Adrenal haemorrhage is sometimes reported. Brooke and Boggs (1951) comment that the pathological findings can all be secondary to profound shock, apart from those in the skin, bowel and bladder. Fisher (1951) described a microscopic lesion in the pancreas which he believes to be specific. The diagnosis must be confirmed by chemical or spectrographic assay, and the organs usually selected are the liver and brain, in which some authors consider the highest concentrations of boric acid are to be found.

Treatment

Since no antidote is known, the chief remedy is the generous administration of intravenous fluids. This serves a double purpose, encouraging elimination as well as being an important part of the symptomatic treatment. Half-strength Ringer-lactate solution with 5% glucose was used in this case, but plasma or whole blood would be given if shock or haemorrhage were severe. Antibiotics are needed, mainly because of the danger of pulmonary oedema and infection.

The symptomatic treatment may include adrenal cortical extracts and vitamin K, although there is little theoretical justification for the latter. Sedatives will be necessary if fits are severe. They must be cautiously given, because boron compounds are themselves cerebral depressants; in some countries they are still in the therapeutic use for their sedative effect.

Prevention

Our first concern in this paper is with poisoning as it occurs during the treatment of ammoniacal dermatitis. The question at once arises, Why have so few cases been reported when so many babies have been exposed to boric acid in this way? One reason appears to be the varying dosage due to the different methods of use. It is generally advised that the drug should be used solely as a 'napkin rinse', impregnating the fabric with a saturated solution, and no systemic effects have been recorded from this procedure. Most of the poisonings have been caused by the liberal application to the napkins or the skin of powdered boric acid or of borated dusting powder, and the remainder by 10% boric acid ointment. Also there is a wide variation in individual susceptibility to the drug, as can be seen in reports of poisoning by ingestion. These reasons, together with the cases which must have been unrecognized or unreported, can account for the apparent rarity of this type of poisoning. In addition, it is likely that tolerance increases in the later months of life, but this is uncertain.

Clearly, boric acid should not be applied in the form of powder. Ointment is also suspect, although the danger from this source has decreased with the alteration in strength of ung. acid. boric, B.P.; it was reduced from 10% to 1% in 1943. The use of the drug as a napkin rinse may be safe, but so long as this remains in favour, it will not be easy to persuade the public of the danger of the powder. To parents, the latter must appear little different from the impregnation of napkins, and they prefer it because of its simplicity. It would, therefore, be better to discontinue all forms of boric acid treatment of napkin rashes, and to select an efficient alternative from the range of modern antiseptics. A number of these have been employed for the purpose, especially in the United States, and have been tested in powder and ointment form as well as by medication of napkins (Benson, Slobody, Lillick, Maffia and Sullivan, 1949; Niedelman and Bleier, 1950; Pfeffer and Smith, 1950; Stephens, Cook and Heberling, 1952).

Before a substance of this kind can be generally adopted it must be shown to be effective and non-irritant but above all non-toxic, for it is known that a variety of chemicals can cause poisoning in infancy by absorption from the napkins. Methaemoglobinaemia has often been produced by marking ink. Severe haemolytic anaemia has been caused by the penetration of naphthalene through the oiled skin of newborn babies when the napkins and bedding have been stored with moth-balls or naphtha flakes (Schafer, 1951; Johnston, 1952). A 1 in 4,000 solution of mercuric chloride has, in the past, been commonly used as a napkin rinse, but it can no longer be recommended. Being a dangerous poison if accidentally swallowed, it is bound to be displaced when safe and effective alternatives are available. Moreover, the exposure of infants to mercury in any form is now considered unwise, because of the part which it may play in the production of pink disease and toxic nephrosis. Cases of pink disease have been recorded which followed the use of mercurial napkin rinses and were possibly caused by them (McCoy, 1950; Warkany and Hubbard, 1951).

The antiseptics which at present appear most suitable for the impregnation of napkins are the quaternary ammonium compounds. Certain of these have been found to be effective and virtually non-toxic. They are more expensive than boric acid, but for this

purpose the difference in cost is not great. One of them, benzalkonium chloride (Roccal), was the subject of a successful clinical trial by Pfeffer and Smith (1950). Like other quaternary ammonium compounds, it has the notable limitation in that its germicidal efficiency is reduced by the presence of soap. It is, therefore, essential to rinse the napkins thoroughly before soaking them for half-an-hour in a 1 in 80 solution.

Prevention of Poisoning Through Other Uses

The common presence of boric acid in hospitals and the home and the general failure to recognize it as potentially dangerous, have resulted in its being added to infants' foods on a number of occasions. Usually a stock solution is mistaken for sterile water, but sometimes the powder has been confused with dextrose. Twenty-two babies died, out of a total of 47 who were poisoned in a number of accidents of this kind (Willson, 1915; McNally and Rust, 1928; Cross, 1944; Barnum and Opper, 1945; McNally and Rukstinat, 1947; Grant and Wegner, 1948; Gold, 1949; Young, Smith and MacIntosh, 1949; Rubin, Recinos, Washington and Koppanyi, 1949). The fatal dose in early infancy may be no more than 3 g. or 60 ml. of saturated (5%) solution. The drug should, therefore, be carefully labelled, segregated from foodstuffs, and excluded from maternity hospitals and other institutions caring for infants.

It is commonly recommended for the treatment of infantile eczema, in the form of wet dressings, ointment or powder. Poisoning produced in this way has seldom been described, although fatal examples have been recorded by Watson (1945) and Lueck (1949). It should be regarded as a dangerous form of treatment, at least until its toxicity has been fully investigated.

A saturated solution is often used for cleansing the nipples of nursing mothers. It has been suggested, but it is difficult to believe, that dangerous amounts of boric acid may thus be swallowed by the infant. Aikman (1930) mentioned the death of a baby aged 2 days which had been certified as due to poisoning by boric acid 'nursed from mother's nipple, used as a wash'. No details were given, and it appears very unlikely that poisoning was the true cause of death. Nevertheless, this is not a safe procedure. The antiseptic action of boric acid is inadequate for the purpose, and the use of a communal bowl of lotion may actually spread infection. Outbreaks of neonatal diarrhoea affecting breast-fed infants almost exclusively have been described by Lembcke, Quinlivan and Orchard (1943) and Wegman (1951); no specific organism was detected on either occasion, but it was shown that boric acid solution used for breast hygiene was the probable vector of infection.

Preparations of borax or of boric acid are in common use for the treatment of thrush in infancy. Borax (sodium borate) can produce the same toxic effects as boric acid, and although poisoning by borax is very rare, its potential toxicity is worth remembering. One palatable preparation, borax and honey (mel boracis, B.P.) is liable to be given in excess, and has caused the serious poisoning of one infant (McWalter, 1907) and the death of another (Birch, 1928) when large quantities were used.

It has long been realized that boric acid and borax are only feebly germicidal, and Sollman (1948) has questioned whether in fact they check bacteria under clinical conditions. It cannot be denied that boric napkin rinses are usually successful in ammoniacal dermatitis, but the weak bacteriostatic action of the acid may not be wholly responsible. Its very acidity, by neutralizing ammonia, may play a part. Even the belief that boric acid as a topical application causes no local damage to the tissues has now been challenged; Novak and Taylor (1951) found that concentrations greater than 2% inhibited phagocytosis. In general, it is not surprising that Watson's (1945) description of it as a dangerous drug of little value should have been endorsed in this country (*Lancet* annotation, 1950). The elimination of boric acid from clinical practice would cause few regrets, and its everyday use should certainly be discouraged.

Summary

A non-fatal case of poisoning of a young infant resulting from the treatment of napkin rash with powdered boric acid is reported.

The main clinical features were vomiting and diarrhoea, with slight gastro-intestinal bleeding, convulsions and a rash on the face and extremities. This type of poisoning may readily be confused with infective gastro-enteritis.

Both boric acid and mercuric chloride are undesirable substances for the treatment of napkin rash. Safe and effective alternatives are available.

Boric acid is a potentially dangerous drug and is only feebly antiseptic.

We wish to thank Professor R. W. B. Ellis for permission to publish this case, and Sister Jean Wood for the nursing management of it.

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HAEMANGIO-ENDOTHELIOMA WITH HAEMORRHAGE AND THROMBOCYTOPENIA

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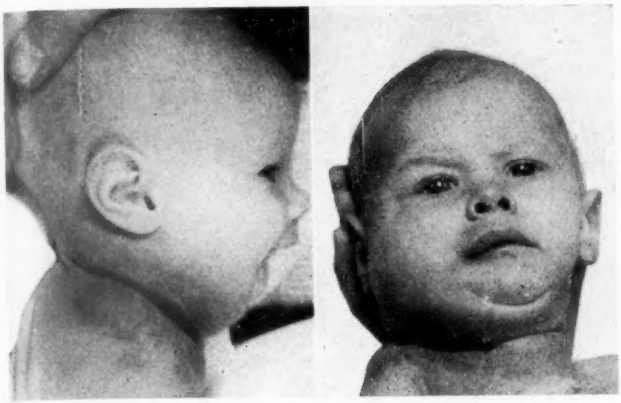
Two infants have recently been observed with haemangiomata into which gross and dangerous bleeding occurred, associated with thrombocytopenia. The naevus, in the form of the port-wine stains and strawberry naevi, is a common benign condition, fading or disappearing with the years and with or without treatment. That it should at times, and in the cases described below, be a menace to life either from haemorrhage or from malignancy raises controversial points in histology.

The association of haemangioma, haemorrhage and thrombocytopenia has already been reported on at least three occasions. Kasabach and Merritt (1940) described such a case in which a purple swelling appeared on the thigh of an infant 1 week old, slowly spreading to involve the buttock and scrotum. At the age of 9 weeks haemorrhage occurred into the swelling, part of which became necrotic, and petechiae were observed over the abdominal wall. Biopsy confirmed the clinical diagnosis of capillary haemangioma. Blood examination revealed increasing anaemia and considerable thrombocytopenia. The platelet count fell to 16,000 per c.mm. and both bleeding and clotting times were markedly prolonged. After several blood transfusions had been given the lesion responded successfully to radiotherapy, and the boy was in good health with a normal blood picture at the age of $2\frac{1}{2}$ years.

In the case of Rhodes and Borrelli (1944) the haemangioma, present at birth, gradually spread to involve the lower part of the head and face, the neck, shoulder and upper part of the thorax on the left side. Haemorrhagic spots were seen around the pharynx and the baby's cry became laryngeal. At 2 months numerous ecchymoses and petechiae were noted all over the body; anaemia was moderate, thrombocytopenia considerable (platelets, 15,000 per c.mm.), and the bleeding time was greatly prolonged. The biopsy pathological diagnosis was haemangio-endothelioma. With treatment by repeated blood transfusions and radiotherapy the size of the tumour lessened and the haematological picture improved. Silver, Aggeler and Crane (1948) describe the case of a female infant with a small vascular tumour behind the right ear at birth. Similar small tumours appeared in other situations later. At the age of 5 months a large tumour was observed on the back, it did not respond to radiotherapy, and gradually spread over a large area of the thorax, shoulder, neck and back of the head. The blood picture, normal at first, later showed anaemia and thrombocytopenia (platelets, 32,000 per c.mm.) with prolonged bleeding time. In the course of the case there were generalized petechiae and ecchymoses, haemorrhages into the substance of the tumour, a large haemothorax and death. Necropsy findings showed an extensive capillary and cavernous haemangio-endothelioma involving skin, subcutaneous tissue, striated muscle, thyroid capsule and parietal pleura.

Case Reports

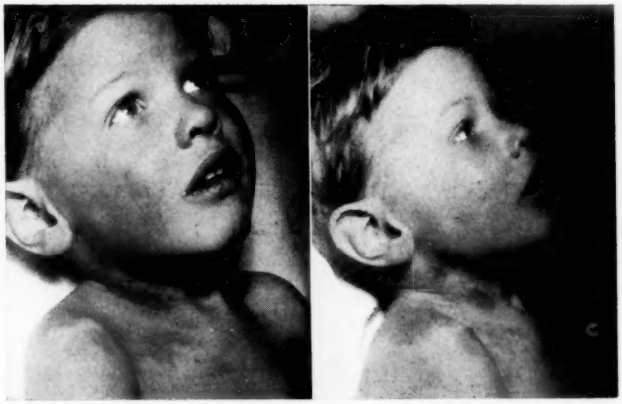
Case 1. Ian K. was born at term on December 24, 1946. The delivery was difficult, but the baby appeared normal at birth, weight being about 6 lb. At the age of 6 days a swelling appeared in the right side of the neck and rapidly increased in size. The overlying skin was a deep purple and this discoloration extended down over the right shoulder. There was no constitutional disturbance and the swelling slowly subsided. The baby was discharged home on the eighteenth day, artificially fed and weighing 5 lb. 10 oz. At 5 weeks old some subcutaneous lumps could be felt in the right side of the neck, and the skin remained slightly discoloured. At the age of 3 months he was re-admitted to hospital as an emergency case with the history that four days previously further swelling and bruising had been noted in the original place, extending over the right shoulder. The swelling steadily increased in size and began to cause respiratory distress. Examination revealed a discoloured swelling like a large haematoma, and occupying the anterior triangle of the right side of the neck, extending up on to the right cheek, over the right clavicle and out over the right shoulder (Figs. 1 and 2). The swelling continued to



FIGS. 1 and 2.—Case 1, aged 4 months, (25.4.47) showing original mass in the neck in antero-posterior and lateral views.

increase in size with further respiratory distress and stridor. Aspiration produced fresh blood. After four days the head and neck were immobilized in a plaster cast, and 100 ml. of blood was transfused. Following the transfusion there was no further bleeding, but the swelling altered little in size and after three weeks in hospital the baby was transferred to St. Bartholomew's Hospital for treatment with deep x-rays. Four local treatments each of 200 r were given. The swelling was somewhat reduced but there was no dramatic change at the time. Three weeks after the last treatment a number of small subcutaneous swellings appeared under the skin on the legs and buttocks. Biopsy and section of one of them showed it to be a small capillary haemangioma without any evidence of malignancy. At the age of 6 months the baby was sent home still with considerable swelling in the neck. Blood examinations are recorded in Table 1. At the age of 9 months he was examined and found to have a large mass on the right side of the neck extending from behind the mastoid process forwards into the neck and over the upper sternum with marked inspiratory recession of the lower ribs. The spleen was not felt though the liver was enlarged (three fingerbreadths). There had been a few fresh subcutaneous haemangiomata on the left side of the abdomen and the left thigh. At 10 months the baby weighed 13 lb. 10 oz. The mucous membranes were pale and the mass was thought to be enlarging. He was therefore re-admitted to St. Bartholomew's Hospital for another course of deep x-ray treatment which this time was followed by great improvement (10 treatments of 200 r, 190 m.v.). Again fresh haemangiomata developed on the limbs during and after this treatment, and there was a slow but steady improvement. At the age of 2 years he weighed 22 lb., but though small was talking and walking and behaving normally. All the subcutaneous tumours had disappeared. At the site of the swelling the subcutaneous tissues had become atrophic and the skin remained discoloured resembling a fading haemangioma. At the age of $3\frac{1}{2}$ years he weighed 28 lb. and seemed to be normal except for the signs described on the right side of the neck (Figs. 3 and 4). At the age of 6 years he is a well-grown, healthy boy but the skin of the right side of the neck is discoloured and atrophic, and there is some limitation of movement of the neck, the head being held over towards the affected side. The radiographs of the neck, chest and shoulder show a peculiar shape of the right clavicle at the age of 9 days (Fig. 5) and later some rarefaction of the outer end of the right clavicle and of the head of the right humerus, together with irregular subperiosteal bone formation (Figs. 5, 6 and 7).

Case 2. Kenneth P. was born on April 10, 1951, following a normal pregnancy and delivery. The birth weight was 8 lb. At birth a large, soft-tissue swelling was noted on the left side of the neck extending downwards over the left shoulder and upwards to the left ear which



FIGS. 3 and 4.—Case 1, aged 3 years 4 months (22.4.50), after treatment showing discoloured and atrophic skin.

TABLE 1

BLOOD EXAMINATION OF CASE 1 (BORN 24.12.46)

Date	Hb % (g.)	R.B.C. (m/c.mm.)	C.I.	W.B.C. (per c.mm.)	Platelets (per c.mm.)	Clotting Time (min.)	Bleeding Time (min.)
25.3.47	84 (11·6)	3·71	1·07	13,750		$1\frac{1}{2}$	$3\frac{1}{2}$
28.3.47	48 (6·6)	2·27	1·09		124,850	1	$2\frac{1}{2}$
8.4.47	53 (7·3)					2	9
16.4.47	70 (9·7)	3·40	1·06	11,000	22,000	2	20
24.6.47	70 (9·7)	3·78	0·9	4,700	50,000		10+
20.10.47	70 (9·7)	3·50	1·0	7,000	4,000	$2\frac{1}{4}$	$9\frac{1}{2}$
28.2.49	92 (12·88)	3·43	1·0	63,000	133,000		
4.4.50	88 (12·32)	4·27	0·9	5,000	298,000	6	$4\frac{1}{2}$

Differential white blood count normal throughout.

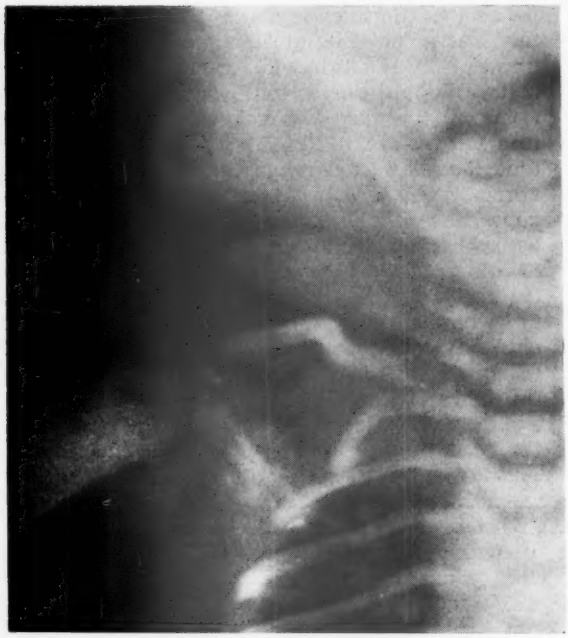


FIG. 5.—Case 1, aged 9 days, showing abnormal clavicle.

was displaced. The consistency of the swelling was soft but there were a number of firm, bluish nodules in its substance. The skin overlying the tumour was markedly oedematous. Associated with the swelling was a degree of micrognathia and the palatal arch was high. Apart from some difficulty in sucking, probably due to the micrognathia, the infant's progress gave rise to no anxiety during the immediate post-natal period. The swelling, which was thought to be a haemangioma, became very much smaller and the baby was discharged home with his mother on the twelfth day of life. The rapid reduction in the size of the tumour appeared to be due to extensive thrombosis within the haemangioma. The tumour remained relatively small and the baby made normal progress until the age of 4 weeks. On May 7 there was a rapid increase in the size of the swelling during the night. When seen next morning the baby was pale and distressed with a slight stridor. On the left side of the neck there was a huge tense, blue haematoma extending upwards to involve the left cheek, mandible and the lower half of the pinna and downwards to the level of the second costal cartilage (Figs. 8, 9, 10). In the neck the swelling crossed the midline anteriorly. Examination of the blood showed prolongation of both bleeding and clotting times (both over 20 minutes) with severe thrombocytopenia (platelets, 10,000 per c.mm.) and anaemia (haemoglobin 52% (7·7 g.%)).

He was given vitamin K, 10 mg., twice daily and at first his condition seemed to improve. The stridor disappeared after 24 hours and some thrombosis appeared to be occurring in the swelling. Four days later, however, the stridor reappeared and the breathing became distressed and irregular. In spite of the usual restorative measures the child died.

Post-mortem examination showed the body of a well-nourished infant. There was a bluish swelling on the left side of the neck as described above. On dissection the haemangioma was found to involve not only the skin and the subcutaneous tissues but the muscles of the neck, the epiglottis, both the true and false vocal cords in the larynx and the surrounding soft tissues. Apart from some basal congestion in the lungs the remaining organs were normal. Death was ascribed to asphyxia. Histological section showed the tumour to be a highly vasoformative haemangio-endothelioma, clearly infiltrating neighbouring muscle (Fig. 11).

FIG. 6.—Case 1 aged 10 months.

FIG. 7.—Case 1, aged 4 years 6 months, showing rarefaction and irregularity of the clavicle.

FIGS. 8, 9, 10.—Case 2, Original mass in the neck with discoloration of the skin.

years ago, the lump having first suddenly appeared five years ago. The right shoulder region was irradiated after the operation.

Haemangio-endothelioma is the name used by the authors whose cases are quoted above. In our fatal Case 2 the histology proves local infiltration into muscle, and the diagnosis is haemangio-endothelioma without metastasis. Our first case raises the problem of metastasis in a new way. Sections of one of the small subcutaneous tumours whose appearance followed radiotherapy shows a typical capillary haemangioma, a diagnosis in

Discussion

The classification of haemangiomata is made difficult by variations in the histological appearances of different parts of the same lesion. In some cases there is undoubted infiltration into neighbouring tissues, establishing the fact of local malignancy. Other cases raise the problem of metastatic spread. A simple solution is to regard the common capillary or cavernous haemangioma as a congenital developmental defect of blood vessels, naming it a hamartoma and contrasting it with a true tumour, the haemangio-endothelioma, which has malignant potentialities of local infiltration, of recurrence and of metastatic spread. When the lesion is first observed there seems no way of making a clinical distinction which must await either the evolution of the case or a biopsy. Stout (1943) after a careful review of his own and of reported cases concluded that he could recognize the true tumour, the haemangio-endothelioma, by finding (1) atypical endothelial cells in greater numbers than were needed to line vessels with a simple endothelial lining, and (2) a delicate anastomosing framework of reticulin fibres outlining vascular tubes though concealed by masses of endothelial cells. In his view metastasis and local infiltration only occur with true haemangio-endothelioma. Among the cases described (Stout, 1943) is one of a man of 25 years with a haemangio-endothelioma in the supraclavicular fossa, successfully excised. Three years after operation metastases appeared in bone and one year later in the lungs. Five years after the original excision the patient died. Mr. J. P. Hosford allows us to quote the case of a girl now alive, well and without sign of recurrence at the age of 11 years from whose right supra-clavicular fossa he excised a haemangio-endothelioma three

FIG. 11.—Section of haemangio-endothelioma with infiltration into muscle × 115.

keeping with the short life of these lesions. Either the patient has a 'tendency' to produce showers of haemangiomata or these were benign metastases. The main neck lesion behaved in a manner so like that of the recorded cases that it is claimed to be a haemangio-endothelioma in the absence of biopsy. In this view the case is one of haemangio-endothelioma responding to radiotherapy by disappearing itself and by producing benign metastases.

In all five cases the haemangioma grew early to a large size. In four the site was the soft tissues of the neck, like the possibly related condition of cystic hygroma. In the two that have come to necropsy invasion of deeper structures has caused death. In two of the surviving cases the respiratory tract was obviously obstructed, presumably from pressure or invasion.

Radiological and clinical signs of bone involvement were present in Case 1 and in the case of Kasabach and Merritt (1940). Pack and Miller (1950) state that a haemangioma next to a bone may produce either erosion or local overgrowth, but the changes might have been due to the x-ray treatment given.

Thrombocytopenia with prolonged bleeding time was present at some stage in all five cases, associated with purpura and gross haemorrhage into the tumour substance. In our second and in Kasabach and Merritt's case the clotting time was prolonged, possibly owing to a vitamin K deficiency. The cause of the thrombocytopenia according to Silver *et al.* may be a failure of the megakaryocytes, which they observed to be somewhat agranular and increased in numbers in the bone marrow. In their case the platelet count was normal during the first 20 months of life and in Case 1 and in that of Kasabach and Merritt the platelet count returned to normal. These findings are against a congenital platelet deficiency, and possibly the process is invasion of the blood vessels by the tumour growth causing haemorrhage so that platelets are used up in the network of the haemangioma, leaving fewer available for the general circulation. The thrombocytopenia and prolonged bleeding time must add greatly to the risks of pressure effects on vital structures, notably the respiratory tract, from sudden enlargement of the haemangioma.

In three of the four cases treated deep x-ray treatment appeared to be effective in reducing the size and encouraging the disappearance of the haemangioma. Blood transfusions were also required to counter anaemia and to lessen the risk of further haemorrhage.

Summary

Two cases are described in which haemangio-endotheliomata in the neck were associated with thrombocytopenic purpura. In both cases haemorrhages occurred into the tumours producing serious respiratory embarrassment. Three similar cases from the American literature are briefly reviewed. Features common to the group are rapid enlargement, invasion of the deeper structures, and x-ray changes in underlying bone, recurrent haemorrhage, an accompanying thrombocytopenic purpura, anaemia and prolonged bleeding and clotting times, sensitivity of the tumour to x-rays and perhaps a predilection for the tissues of the neck.

We are grateful to Professor G. F. Hadfield for his advice and help in the gathering together of the material for this paper.

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A HISTORY OF INFANT FEEDING

PART V.—NINETEENTH CENTURY CONCLUDED AND TWENTIETH CENTURY

BY

IAN G. WICKES

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The Study of Scurvy in the Nineteenth Century

In spite of the fact that scurvy has been known to medical writers since the days of Hippocrates, there is remarkably little reference in the literature to this disease as it occurs in infants. Sea-scurvy, of course, was for centuries the disease dreaded by all mariners, and opinion seems to have been more or less evenly divided in the eighteenth century as to whether sea-salt and salted foods or the lack of fresh fruit and vegetables was the causative factor. There is good evidence also that scurvy was prevalent amongst the poor in the towns for it was described by Gideon Harvey, physician to Charles II, as 'Scorvey, the Disease of London' in 1675. Harvey's account is almost entirely confined to the disease in adults, but he believed that it was contagious and that infants contracted it from kissing. Glisson, as we have seen, was clearly aware of the separate identities of scurvy and rickets, but for the next 200 years and more the few references to the disease in the paediatric literature were disguised under the title of 'acute rickets'.

In 1878, however, W. B. Cheadle reported in the *Lancet* three cases of scurvy supervening upon rickets, preceded by a lengthy and learned discussion on the probable aetiology of the disease, that marked a great advance in medical thought. Cheadle summarized the previous views, all of which had rated scurvy as a deficiency disease. Thus Baly had suggested that it was due to a lack of certain organic acids, Garrod to a lack of potash, and Buzzard to a combination of both, whereas Rolfe had resurrected the ever-popular acidity theory expressed in terms of diminished alkalinity. Cheadle discarded the current belief in cold and lack of sunlight as causative factors because the disease was as well known in the tropics as amongst arctic explorers, and he emphatically stated that 'the essential factor is the absence of certain elements in the food'. Furthermore he knew that these elements existed in fruit, fresh milk and potatoes. Incidentally, potatoes were first introduced into this country by Sir Walter Raleigh in 1585 but they did not become popular for at least a century to follow, but thereafter their increasing use in the feeding of infants probably considerably reduced the incidence of frank scurvy amongst the children of the poor until the production of condensed milk and patent foods once more accounted for an increase during the nineteenth century.

Cheadle's three cases were aged from 14 months to 3 years and all were well cared for apart from the diet. The first was breast fed with supplementary feeds of condensed milk for six months and then weaned on to oatmeal, rusks and broth without any milk at all until the advent of frank scurvy with fungating gums at 14 months. On this Cheadle made the classic comment: 'The diet was more than a rickety diet—it was a *scurvy* diet'. For treatment he recommended two pints of 'new' milk daily, half an ounce of raw meat juice, steel wine, potassium bromide and cold sponging. His second case was hand reared on milk alone for 10 months and then on bread and patent foods until scurvy became pronounced at 16 months, and the third case, aged 3, had received no milk, meat or vegetables since weaning at the age of 2. Cheadle wondered, just as many medical men subsequently did at the beginning of World War II, whether the many cases of gingivitis he saw were really suffering from a mild degree of the scorbutic state.

In 1883 Barlow collected 20 cases of 'acute rickets' from the literature, added 11 of his own, and fully described the disease which subsequently became known as Barlow's disease, but he fully acknowledged the earlier recognition of infantile scurvy by Ingerslev and Cheadle. He pointed out that the disease mainly affected children under 2, that it was more prevalent in winter, and that active rickets was often present concomitantly. His main contribution, how ever, was to describe fully the pathological findings, including the characteristic

sub-periosteal haemorrhages. Like Cheadle, he was fully aware of the importance of diet and one of his cases, a boy aged 15 months, had been fed on Robinson's groats, Swiss milk, baked flour, condensed milk, Robb's biscuits, Liebig's extract and saccharated lime water in turn since being weaned at the age of 6 weeks. He concluded by observing that 'infant foods cannot be trusted as the sole aliment for any lengthened period'.

In spite of these enlightened contributions from Cheadle and Barlow, it was some time before the disease was generally recognized in infancy. Samuel Gee, their colleague, described cases in 1880 under the heading 'Osteal and Periosteal Cachexia', and for many years 'scurvy-rickets' was a popular clinical hotch-potch diagnosis. The aetiology of scurvy was finally put on a sound scientific basis by the discovery of vitamin C by Hopkins and later the synthesis of ascorbic acid by Györgyi in 1928 made specific therapy a practical possibility.

During the twentieth century the incidence of infantile scurvy has steadily declined, yet in 1935 Still had collected 155 personal cases with a mortality of 5·5% compared with Barlow's 22%. There was naturally a rise in incidence in World War I but the provision by the Government of cheap bottled orange juice and the free use of ascorbic acid tablets in the infant welfare clinics in the second World War prevented a similar occurrence and the condition is now a rarity.

The Incidence of Rickets in the Nineteenth Century

A summary of the early history of rickets up to Glisson's account in the seventeenth century has already been made. As the Industrial Revolution progressed the employment of women and children, and the popularity of starchy foods for infants, taken in conjunction with the overcrowded and squalid slum conditions, inevitably resulted in a rise in the incidence of the disease in the towns. Even by the middle of the eighteenth century, however, James Nelson (1753) wrote that 'Rickets is a Distemper extremely common in London', and a century later Gee (1868) computed that 30% of the children admitted to The Hospital for Sick Children, Great Ormond Street, under the age of 2 were rickety; nor was this disease solely confined to the children of the poor. Gee attempted to stimulate medical interest in the condition for it seems that rickets were still largely accepted as the normal state in late infancy at this time. Cheadle had observed that in 1865 the winner of a baby show was obviously markedly rachitic.

The high incidence of rickets was continued into the twentieth century, for in 1902 in Leeds 50% of the babies were stated to show well-marked signs of the disease, and a further rise in the rate took place during and after World War I, particularly in Vienna where, in 1919, Dr. Harriette Chick led an expedition of research workers. They succeeded in convincing Professor von Pirquet, who was previously of the opinion that rickets was an infection, of its true nature as a deficiency disease. In war time, unfortified margarine had been a potent cause of the epidemic.

Speculation as to the cause of rickets has naturally been widespread. At the outset of the nineteenth century William Buchan expressed the opinion that the recent increase in the manufacturing towns was due to lack of exercise but later in the century Routh deprecated starch as a food for infants because it interfered with the absorption of calcium and phosphorus from the gut and hence predisposed to rickets. Magendie had shown that dogs die if fed on white bread whereas they thrive on brown, and Liebig had stated that the alum used for bleaching causing a precipitation of the phosphorus and hence the development of rickets. In this respect it is interesting to recall Mellanby's recent work on the development of canine hysteria due to the agene process for bleaching flour.

In 1886 Bland-Sutton observed at the London Zoo that lion whelps and other young animals fed exclusively on raw meat always died of rickets, whereas by feeding them upon milk, pounded bones and cod liver oil instead, without making any alteration in the hygiene or ventilation of their cages, he was able to rear successfully the first lion cubs born in captivity. This work led Cheadle to appreciate the importance of diet in this disease as well as in scurvy, and he initiated the view, which held supremacy for many years, that rickets was a fat-deficiency disease, indeed until Edward Mellanby in 1919 showed by experimental work on puppies that the dietary rachitogenic factor could be narrowed down to a fat-soluble substance separate from vitamin A. The final challenge to this view came from Leonard Findlay, writing in the *Lancet* in 1922, who revived the old theory of lack of exercise. He observed that although Indians of all castes notoriously lived on a low fat intake, rickets was seldom seen except amongst the wealthy, from which he concluded that the physical restrictions of purdah were responsible. In fact of course, lack of sunlight rather than of exercise was responsible, as it was also in Findlay's puppies who became rickety on a low-fat diet in the towns but not in the country. Nowadays there is no serious challenge to the view that rickets is due to a deficiency of the fat-soluble vitamin D.

Curiously enough cod liver oil has been used empirically for the prophylaxis and treatment of rickets for well over a century. J. H. Bennett (1841) recorded that oleum jecoris aselli was first used in 1766 in the Manchester Infirmary for the treatment of rheumatism and allied conditions, and that it had been used traditionally in Scotland for the prevention and cure of rickets. Early in the nineteenth century it had been used extensively in Holland and Germany where Dr. Schenk had recorded several cures by the administration of one or two ounces daily. By 1840 a few London physicians were obtaining good results with it and Bennett believed that the combination of rickets and scrofula responded particularly well due, he thought, to the trace of iodine contained in the oil. This marked the addition of a most useful weapon to the average physician's armamentarium, for Nelson had had to be content in 1753 with recommending a cold bath as 'the great and noble Remedy for this Disease' together with bleeding and purging if fever was also present, but by 1868 Gee had accepted cod liver oil as a 'noble remedy' and thereafter it became increasingly popular, aided by the manufacture of more purified, and therefore more palatable, preparations. Nevertheless even such an authority as Eric Pritchard (1904, 1916) failed to make any mention of its use and value in either of his two books on infant feeding. However, the provision of free cod liver oil by the Government during and after World War II has convinced even the most sceptical lay opinion of its value and hence florid rickets is nowadays rarely seen.

The Contribution of the Nineteenth Century

As the seventeenth century unfolded, the old scholastic conservatism, with its ancient humoral pathology, was gradually superseded by the steady advance of a more practical and experimental approach to scientific problems in general, and medical problems in particular. During the eighteenth century the dawn of modern medicine, with its central conception of disease entities, began to break and grow but at first medicine lagged behind the physical sciences and the art of infant feeding scarcely felt the new scientific influence at all.

The first impact, however, was made when the 'chymical' analysis of milk at the outset of the nineteenth century became a practical proposition though the advantage gained was not, for many years, very great. It was helpful, of course, to know that ass's milk was the nearest approach to breast milk, and that cow's milk required modification in order to be 'humanized', but this in fact had been deduced empirically some years previously. In spite of this advance infants were all too frequently reared, or killed, on a diet of flour and water in the first half of the century. During this period the supervision of infant feeding, when indeed it was supervised at all, was in the hands of midwives and obstetricians who were reluctant, to say the least, to abandon the folklore approach which had been traditional for so long. Liebig seems to have been the only true scientist of note to enter the field of infant nutrition but his food for infants was by no means an unqualified success.

The rapid fall in infant mortality which took place during the latter half of the eighteenth century was carried over for a time into the nineteenth, but for the major part of the century it remained static about the 150 mark, and even sustained a slight rise in the 1890s though the general death rate for the whole population fell steadily from 1850 onwards. It is generally agreed that the high rate was largely dependent upon the prevalence of gastro-enteritis, which in its turn was a product of faulty feeding, bad hygiene and poor management. The advent and elaboration of dried and evaporated milks and the mass production of teats and feeding bottles apparently did little or nothing to bring about an improvement, for the apparent increase in rickets and scurvy was probably mainly due to their increasing use. This was disappointing, for John Clarke (1815) had hoped that society would benefit if wet nurses could be dispensed with; he had argued that the nurse's own child was left at home to be hand reared under bad conditions whereas the employer's child, who would have stood a better chance of survival on artificial feeding, was reared on the breast.

The knowledge of the composition of cow's milk resulted in the publication of numerous formulae and complicated systems such as that introduced by T. M. Rotch of Boston who believed that minute variations in the composition of a feed, even 0·1% variation in a single food element, would make the difference between its being digested or not (Morse, 1935). The percentage system of feeding insisted upon the very careful graduation of the size and composition of the feeds from week to week with a result that milk was prescribed with the same accuracy and precision as a dangerous drug! But perhaps the acme of complexity is to be found in Tuley's book of 1904 (Levinson, 1926) which contained two and a half pages of algebraic formulae for calculating a healthy baby's feed.

Perhaps the greatest benefit to the safety of infant feeding accrued from the public health movement under the auspices of Simon and Chadwick which lessened the danger of the transmission of diseases by milk and water and gradually raised the general

standard of living conditions. Towards the end of the century the work of Pasteur and Koch drew attention to the danger of micro-organisms in milk and for this reason Budin scorned the elaborate humanizing formulae and instead relied entirely upon the use of sterilized undiluted cow's milk when breast milk was not available.

The paediatric literature was mainly concerned with the rapid advance in the knowledge of children's diseases, and for a while infant feeding remained in the doldrums. Thus the sixth edition of William Buchan's text-book (1769) attributed the high infant mortality to 'improper management and neglect" and to the 'absurd and ridiculous practices' which were so different from the natural methods of animals who were 'guided by instinct, while man, trusting solely to art, is seldom right'. Yet the twenty-second edition (1832) showed no notable advance over the 50 year period in the section on infant feeding, though there was a remarkable expansion of the rest of the book which was concerned with diseases and their treatment.

Since Armstrong's dispensary closed in 1781 there was no organized medical care for children until Davis founded his dispensary in 1816, but paediatrics as a real and separate specialty scarcely existed before the middle of the century when The Hospital for Sick Children was founded at Great Ormond Street. Thereafter Samuel Gee, Charles West, Eustace Smith, Goodhart and Cheadle greatly added to our knowledge of the subject though they were mainly concerned with diseases and only Budin, the obstetrician, notably influenced medical thought on infant feeding. Edmund Cautley, in the preface to the second edition of his comprehensive text-book on the subject at the end of the nineteenth century, noted the recent advance in bacteriology and the percentage feeding system, but he objected to treating the infant's stomach as if it were a test-tube for the reception of alarmingly complicated formulae, and he summed up the general state of affairs at this time when he wrote that 'although the feeding of infants is free from the taint of empiricism, and every year rests on a more scientific basis, it still remains largely an art which gives ample scope for judgment and resource'.

Infant Welfare Movement in the Twentieth Century

The steady reduction in infant mortality during the last 50 years has occurred *pari passu* with the gradual development of the infant welfare movement, and although the child welfare clinics are by no means solely a beneficial influence, yet there can be no doubt that the education of the mothers with regard to the value of breast feeding and the proper use of dried milks, together with the distribution of vitamins and cheap powdered milk, have been a major factor in the general improvement.

In 1892 Pierre Budin founded the first welfare clinic, the *Consultation de Nourissons*, where breast feeding was ardently encouraged and sterilized cow's milk was issued in sealed bottles, one per feed. The babies were examined and each mother was provided with a card showing the date of birth, weekly weight chart and the mode and quantity of feeding. Two years later at Fécamp Dr. Dufour independently founded the *Goutte de Lait* from which was issued diluted milk with cream and sugar added. Thereafter this movement spread rapidly throughout France.

In 1899 Dr. Drew Harris, inspired by Dufour's work, set up the first English milk depot where, in addition to the issue of milk at a financial loss, weekly weighings were carried out. The first real consultation clinic was set up at the Battersea Milk Depot by Dr. McCleary in 1905 (Pritchard, 1916, and McCleary, 1933), and thereafter the movement rapidly developed in this country also so that about 200 largely voluntary societies were functioning by 1913, which was increased to 650 by 1915, and 1,278 at the end of World War I, a remarkable growth for war time. Statutory powers were given to the local authorities to establish clinics in 1909 and these were extended by the Maternity and Child Welfare Act of 1918.

The first international congress on *Gouttes de Lait* took place in Paris in 1903 when the rival interests of obstetricians and paediatricians were publicly displayed, the former asserting that the clinics were encouraging artificial feeding at the expense of breast feeding. A national conference on infant mortality in London in 1906 further stimulated medical interest in this pressing problem and in 1928 the founding of the National Council for Maternity and Child Welfare under the chairmanship of Dr. Pritchard marked a further step forward in the organized attack to improve the standard of infant care and management.

Health visitors first began to be employed at the beginning of this century (Craig, 1946) and by 1905 50 authorities were using them to establish a liaison between the homes and clinics, a much needed task for in Liverpool the infant mortality in the centre of the town was more than twice that in the suburbs. Their work was greatly simplified by the Notification of Births Acts of 1907 and 1915 which made early visiting at first a practical possibility and later the universal custom. The problem of illegitimacy was also tackled by the foundation of the National Council for the Unmarried Mother and Her Child in

1918, though the Scottish Committee was not set up until 1940.

Thus it will be seen that the infant welfare movement, which was originally instituted by the zeal and funds of voluntary workers, has been gradually extended by legislation and public grants until the vast organization, which now reaches every hamlet in the United Kingdom, was built up. A very high proportion of working and middle class mothers now avail themselves of the facilities offered and the standard of mothercraft has greatly improved. However, since the advent of the National Health Service the justification for the separate existence of the movement no longer exists. The poor mother no longer has to think of the cost when she consults her general practitioner, who now, for the first time, has the opportunity of becoming a true family doctor. Logically, therefore, as Moncrieff (1950) has said, the family doctor should be carrying out the work in the homes and in the infant welfare clinics, assisted by the health visitors. This merger with the general medical services will probably be the final stage in the evolution of the infant welfare movement.

Frederick Truby King (1858-1938). This outstanding and remarkable man was for many years Superintendent of the Seacliff Lunatic Asylum near Dunedin, New Zealand, an enlightened institution whose inmates enjoyed occupational therapy in the surrounding gardens and adjoining farms. Truby King was a keen student of plant and animal life and he became particularly interested in the scientific feeding of calves and the reduction of the incidence of scouring amongst them. He himself suffered from phthisis and while on sick leave in Japan in 1904 he became impressed by the popularity of breast feeding there as compared with New Zealand, and by the good physique of the general population. On his return home in the following year he and his wife adopted a daughter, Mary, who in 1948 published his biography. They resolved to improve the practice of infant feeding first by encouraging breast feeding and failing that by educating mothers and nurses in the use of suitable substitutes.

In 1907, at the age of 49, he started the Truby King movement earnest and the Plunket Society, named after the Governor of New Zealand, was formed. At the same time King installed at his week-end cottage at Karitane 13 of the worst cases of unwanted babies he could find, and there, by skilled care and attention to feeding, he proved that they could be reared and brought up to become normal useful citizens. The Mothercraft Movement rapidly developed in New Zealand so that quite soon 80% of the mothers were attended by Plunket nurses and the infant mortality, which in 1900 was already only half that in England, was halved again by 1912. The nurses were taught to encourage breast feeding, to guard against overfeeding at all costs, to use a modified form of percentage feeding with cow's milk, to learn how to collect representative samples of breast milk and to estimate the fat content, in addition to all the other aspects of mothercraft.

In 1913 Truby King visited England as the New Zealand representative to the Infant Welfare Conference. It seems that he regarded himself rather as a crusader or missionary to a primitive land and, not unnaturally, this attitude resulted in him being variously regarded as a crank, quack, enthusiast or rival, but a few became his most earnest and faithful disciples. He was determined to prove that apparently weak babies were well worth saving (infant life was still valued much lower than it is today) and that slum mothers were not necessarily slut mothers. To do this he set up a clinic in Bethnal Green where he found that feeding problems were much the same as they were in New Zealand. Later he visited von Pirquet in Vienna who impressed upon him the great danger of overfeeding, and Finkelstein in Berlin who was treating infantile infections dietetically.

In 1917, on his way to Europe again, he visited New York where he was royally received—in marked contrast to his cold reception here. On this visit he founded the Mothercraft School which existed until recently at Cromwell House, Highgate, and he first became acquainted with Marylebone cream (50% emulsion of linseed oil) which Pritchard was adding to sweetened diluted cow's milk. On returning to New Zealand, where he became Director of Child Welfare, he set up factories for the production of 'kariol' (50% fat, 40% sugar and 10% water) and 'karilac' (60% lactose, 35% dextri-dextrose and 5% gelatine) which were subsequently distributed in this country from Cromwell House.

On his third visit to England in 1928 Truby King had become rambling, senile and dogmatic so that the cause he had founded suffered some discredit. It has aptly been written of him:

> 'He was of course a genius. . . . What he gained in pure mental intellect he lost in emotional balance, and, as the normal dissolution of old age came on, the imbalance was accentuated.'

Considerable space has been devoted to the life of Truby King because he was such an outstanding personality of world-wide renown in the first quarter of the present century. At that time his encouragement of breast feeding, with the use of such slogans

as 'breast fed is best fed', was a welcome reminder to all that the recent advances in the production of artificial milks and patent foods in no way superseded the tremendous value of the natural method. His work was marred by his gross over-emphasis of the dangers of overfeeding, which he described as more common and more dangerous than underfeeding in the breast-fed infant, and his influence in this direction is still plainly discernible in England and New Zealand today. It is curious that a man so interested in nature should have insisted on such a rigid restriction of quantity and such a strict adherence to feeding by the clock when it is so plain for all to see that nature obeys no such man-made laws.

Most twentieth century writers have ignored Truby King though his disciples have continued to put his principles into practice and to use his products almost without alteration to this day. His methods have been openly challenged by Pritchard, and Burgess (1925) was at pains to expose the defects and limitations of his system in the treatment of difficult feeding problems. In summary, we find that the Truby King movement has many of the characteristics of a religious revival. The first enthusiasm, inspired by the magnetic personality of one man, was undoubtedly responsible for a great re-awakening of interest in breast feeding and a general raising of the standard of mothercraft as a whole. Unfortunately, as is so liable to happen, his followers have been more concerned with perpetuating his teaching than with making further progress forward. In fact it is sad but true that very little remains of the movement in England today apart from strict enforcement of feeding times and habit training and a morbid fear of overfeeding; when executed with ardour, these precepts are prone to produce a hungry and frustrated baby.

Eric Pritchard (1864-1943). Pritchard, who was medical director of the Infants' Hospital, Vincent Square, was actively engaged in developing the infant welfare movement when Truby King first visited England. He initiated the first infant welfare clinic in London at Marylebone and was the first paediatrician appointed to Queen Charlotte's Hospital.

Although probably a difficult man to work with, comparison of his two books on infant feeding, written in 1904 and 1916, shows that Pritchard was very ready and willing to change his views should they prove to be incorrect. Thus, in the earlier work he wrote: 'there is no sort of coordination between the supply on the part of the mother and the demand on the part of the child', but in 1907 Budin's work was published in England which caused him to revoke entirely the above statement in his later lectures. At the time when he wrote, Rotch's elaborate scheme was in vogue and although he fully acknowledged the excellent work carried out by the Walker-Gordon Laboratories in the production of clean, standardized milk, he also realized that a much more simple and less expensive scheme was necessary and desirable. He therefore devised a 'physiological nursery chart' incorporating weight tables, formula changes at monthly intervals (instead of weekly), total quantities and time intervals between feeds. However, in the later work, he had realized he had been guilty of producing too rigid a scheme for he wrote:

> 'Although in the past I have been guilty of drawing up many a table for the feeding of infants of various ages, I now fully admit that such tables are worthless, unless other important considerations, such as those of clothing, housing, and airing, are simultaneously taken into consideration.'

It is notable that in neither case was Pritchard particularly concerned with the infant's weight as a basis for calculating a feed, being more influenced by the age, but it is encouraging to find a physician at that time attempting to make the feeding schedule fit the baby instead of the reverse. He made a special study of 'test feeds', a term he coined himself, and he noted the great variation which was liable to occur from feed to feed. He accepted the figure of 99 cal. per kg. body weight for the daily food requirements of infants under 3 months, and on this basis he considered that such a baby would require about 2 oz. of milk per lb. weight daily—'hedging myself in with all possible reservations' as he put it (1916). The modern teaching of infant feeding in England today, including its good and bad points, owes a great deal to the foundations laid down by Eric Pritchard who, for a quarter of a century, was actively engaged in teaching and lecturing nurses and students.

Conclusion

In some ways this historical review might be regarded as a chronicle of man-made errors, for many of the ideas in the writings that have been quoted were intended to be an improvement upon nature though few have succeeded. Those who have heeded nature any way, namely the nursing mothers, have seldom found it necessary to put pen to paper. To some extent, however, lactational failure is to blame, for it has been in the search for a suitable substitute for breast milk that so much artificiality has been unnecessarily introduced and this has even spread to engulf the simple act of successful breast feeding itself.

Overfeeding has been repeatedly cited as the main

source of feeding troubles whereas in reality improper feeding (e.g., too early introduction of starch, lack of vitamins, bacterial contamination etc.) has been the chief cause. This attitude reached a peak at the end of the nineteenth century when Budin, Czerny, Finkelstein, von Pirquet, Rotch and Truby King were preaching about the dangers of overfeeding all over the world. In France Budin's influence was so widespread that Cran (1913) reported in 1913 that the weighing machine had become an instrument of torture as much to the mother with plenty of milk as to the one whose lactation is poor. A recent investigation (Wickes, 1952) showed that in London today similar conditions prevail. In this respect we are still fighting a battle that has already been won.

It is, perhaps, in the study of feeding times that the changes in infant feeding habits can best be followed through the ages. In the natural state the infant is fed as often as he is hungry and until his hunger is satisfied, but even in the most primitive civilizations this method may have to be modified by circumstances. Thus, in some parts of China the mothers refer to their offspring as 'one', 'two' or 'three furrow babies' meaning that whereas one will require feeding after the mother has had time to hoe only one furrow, another will be content to sleep at the edge of the paddy field until three have been worked.*

In Tudor times and after no mention was made of a regular feeding schedule. Indeed in the sixteenth century Guillemeau specifically wrote that 'it is fit he should have the teat as often as he crieth'. Cadogan in 1748 seems to have been the first writer of importance to extol the virtues of regular feeding, advising that for the breast-fed infant 'four times in four and twenty hours will be often enough to give it suck' at stated times, the same every day. For hand fed infants 'little and often' became the rule, so well exemplified by the following extract from the *Monthly Repository* (1810):

> **Nursery Clock**
> In the year 1760, Lady Arabella Denny presented a clock to the Dublin Workhouse, to be put up at her expense, in the nursery for foundling children, with the following inscription, viz. "For the benefit of infants protected by this hospital, Lady Arabella Denny presents this clock, to mark, that as children reared by the spoon must have a small quantity of food at a time, it must be offered frequently; for which purpose this clock strikes every twenty minutes, at which notice, all the infants that are not asleep, must be discreetly fed".'

During the nineteenth century writers became increasingly anxious to limit and regulate feeds, frightened as they were by the appalling mortality from gastro-enteritis. Thus, Eustace Smith (1878) recommended 10 two-hourly feeds daily for the first six weeks of life! At the beginning of the present century the pendulum began to swing the other way, Truby King pointing out in 1915 that these frequent feeds resulted in the one thing they were designed to obviate, namely overfeeding. Rigidity, however, was not relaxed. The twelfth edition of Goodhart and Still's text book (1925) recommended a change from two to three-hourly feeding when practicable but insisted that 'whatever interval suits the infant best is to be *strictly* enforced.'

Between the world wars the first signs of the emancipation of medical writers from the strict regime of the past began to be apparent in the papers of Weinfeld and Floore (1930), Clara Davis (1935) and Gesell and Ilg (1937). Later the work of Aldrich and Hewitt (1947) did much to popularize the self-demand or self-regulatory method. When this regime becomes universally adopted, as it surely will, so the last chapter on the history of infant feeding will be concluded. Indeed, such a history would never have been written if Sainte-Marthe's sound advice in his poem Paedotrophia (1584) had been heeded:

> And I, for suckling, no fix'd hour prescribe;
> This Nature teaches best the nursing tribe:
> Let her your mistress be; and when, with cries
> The hungry child demands his due supplies,
> Forbear not you the wish'd relief to bring,
> But, for his use, unlock the sacred spring;
> Nor then be loath your snowy breast to bare,
> That he may suck, and streaming fragrance share.'

This history formed part of an M.D. thesis at the University of Cambridge in 1951. It could not have been written without making full use of the excellent facilities so freely available at the Wellcome Historical Medical Library, and I am greatly indebted to the Director and the librarians for their help.

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INDEX TO VOLUME XXVIII

A

A.C.T.H., and cortisone therapy of congenital hypoplastic anaemia (Diamond-Blackfan type), 363
—— in nephrosis, 372
—— in treatment of acute acquired haemolytic anaemia in childhood, 87
—— —— of nephritis, increased haematuria during, 213
—— —— of Schoenlein-Henoch syndrome, 57
Acidosis, renal, idiopathic, in twins, 55
ADAM, H. M., and MITCHELL, R. G.: Urinary excretion of histamine in children, 61
Adrenergic blocking agents, response of acute anterior poliomyelitis to, 381
Adrenocorticotrophic hormone in treatment of acute acquired haemolytic anaemia in childhood, 87
—— —— —— of nephritis, increased haematuria during, 213
—— —— —— of Schoenlein-Henoch syndrome, 57
AITKEN, J.: Remnants of the vitello-intestinal duct, 1
Alkalosis resulting from overdosage of citrate mixture, 55
ALLEN, F. M. B., *see* FISHER, O. D., and ALLEN F. M. B.
Amino-aciduria and idiopathic hypoproteinaemic oedema in infant, 104
Anaemia, haemolytic, acute acquired, in childhood treated with A.C.T.H., 87
——, hypoplastic, congenital (Diamond-Blackfan type), 363
Antibiotics in treatment of Gastro-enteritis (*abstract*), 242
——, sensitivity to, of strains of *Bact. coli.* associated with infantile gastro-enteritis, 30
Antibody production, failure of, and absence of serum gamma globulin in fatal generalized vaccinia, 110
APLEY, J.: The infant with stridor, 423: (*abstract*), 244
ARNEIL, G. C., and WILSON, H. E. C.: A.C.T.H. in nephrosis, 372
Ascaris infection, treatment with velardon, 329
Ascites, foetal, 398
Atelectasis, pulmonary, in young children, 170

B

B.C.G. vaccination in newborn (*abstract*), 246
BABER, M. D.: Case of osteomyelitis of all the small bones of hands and feet, 24
Bact. coli., strains of, associated with infantile gastro-enteritis, sensitivity to antibiotics, 30
BEKIUS, H., *see* JONXIS, J. H. P., and BEKIUS, H.
Blood glucose pattern of normal infants in first 12 hours of life, 134
—— pressure, estimation of, in childhood with special reference to choice of standard cuffs, 268
—— sugar studies on premature babies, 194
BODIAN, M.: Some observations on children with cytomegalic inclusions (*abstract*), 245
——, *see also* KEMPTON, J. J., and BODIAN, M.
Bone age and development, variations in, in congenital hemihypertrophy, 321
—— lesions, typhoid, in infancy, 19
BOOK REVIEWS: BODIAN, M., *ed.*: Fibrocystic disease of the pancreas, 1953, 342: CRUICKSHANK, E. W. H.: Food and nutrition, 2nd edition, 1951, 79; FALKNER, F.: The convalescent child, 1952, 79; FANCONI and WALLGREN's Textbook of paediatrics, 1952, 160; GARROD, BATTEN and THURSFIELD's Diseases of children, 5th edition, 1953, 159; ILLINGWORTH, R. S.: The normal child, 1953, 341; KRAYNEBÜTH, H., and RICHTER, H. R.: Die zerebrale Angiographie, 1952, 80; LOW, A.: Growth of children, 1952, 341; MOENCH, L. G.: Office psychiatry, 1952, 160; MORRISON, S. D.: Human milk, 1952, 341; 1952 Yearbook of pediatrics, 160; ROVIRALTA, E.: Les vomissements du nourrisson, 1952, 342; RUSSELL, W. R.: Poliomyelitis, 1952, 79; SLOBODY, L. B.: Survey of clinical paedriatrics, 1952, 159; WORSTER-DROUGHT, C., *ed*: Residential speech therapy, 1952, 80
Boric acid poisoning in infancy arising from treatment of napkin rash, 484
BOUND, J. P., and HACKETT, W. R.: Idiopathic hypoproteinaemic oedema and amino-aciduria in infant, 104
——, *see also* FINLAY, H. V. L., and BOUND, J. P.
BOWER, B. D., GERRARD, J. W., D'ABREU, A. L., and PARSONS, C. G.: Two cases of congenital mitral stenosis treated by valvotomy, 91
BRAILSFORD, J. F.: Some radiographic manifestations of early scurvy, 81
BRIGGS, J. N., EMERY, J. L., and ILLINGWORTH, R. S. Congenital stippled epiphyses, 209
——, *see also* PHILPOTT, M. G., and BRIGGS, J. N.
British Paediatric Association, 24th General Meeting, 241
BURRELL, J. M.: Comparative study of circulating eosinophil level in babies. II. In full term infants, 140

C

Camphor, poisoning by, in childhood, 475
CARTER, F. S., and DOCKERAY, G. C.: Case of congenital hemihypertrophy showing variations in bone age and development, 321
Ceylonese children, atypical pneumonias in, 176
CHARLES, D.: Retroperitoneal teratoma in infancy, 147
Chloramphenicol, absorption of, in newborn, 66
Chondrodystrophy with ectodermal defects, 14
Cirrhosis, hepatic, associated with fibrocystic disease of pancreas, 343
Citrate mixture, alkalosis resulting from overdosage of, 55
CLAIREAUX, A. E., *see* DOUGLAS, D. M., and CLAIREAUX, A. E.
CLARK, C. D., and PICKUP, J. D.: Haemorrhagic infarction of kidney treated by nephrectomy, 302
COLES, B. L., *see* MACRAE-GIBSON, N. K., and COLES, B. L.
COORAY, G. H., *see* DE SILVA, C. C., and COORAY, G. H.
Cortisone and A.C.T.H. therapy of congenital hypoplastic anaemia (Diamond-Blackfan type), 363
—— treatment of nephritis, increased haematuria during, 213
—— —— of Schoenlein-Henoch Syndrome, 57
CRAIG, J. O.: Poisoning by volatile oils in childhood, 475
—— and FRASER, M. S.: Accidental poisoning in childhood, 259
CREERY, R. D. G., and PARKINSON, T. J.: Blood glucose changes in newborn. 1. Blood glucose pattern of normal infants in first 12 hours of life, 134

Cretinism, goitrous, radio-active studies in (*abstract*), 243
Curtin, M.: Neonatal diphtheria, 127
Cytomegalic inclusions, children with (*abstract*), 245

D

D'Abreu, A. L., *see* Bower, B. D., Gerrard, J. W., D'Abreu, A. L., and Parsons, C. G.
Davies, B. S., Gerrard, J. W., and Waterhouse, J. A. H.: Pattern of haemolytic disease of newborn, 466
De Silva, C. C., and Cooray, G. H.: Atypical pneumonias in Ceylonese children, 176
Death, unexpected, in childhood, association of pulmonary thrombosis with, 187
Diabetes, congenital, 297
Diamond-Blackfan type of congenital hypoplastic anaemia, 363
Dibenamine, response of acute anterior poliomyelitis to, 381
Diggle, J. H.: Favism in London, 369
Diphtheria, neonatal, 127
Diphtheria-pertussis inoculation, encephalopathy following, 149
Dobbs, R. H.: Treatment of gastroenteritis with antibiotics (*abstract*), 242
Dockeray, G. C., *see* Carter, F. S., and Dockeray, G. C.
Douglas, D. M., and Claireaux, A. E.: Hodgkin's disease in childhood, 222
Douglas, J. W. B., and Mogford, C.: Results of national inquiry into growth of premature children from birth to 4 years, 436
Drennan, J. M.: Acute isolated myocarditis in newborn infants, 288
Duodenal ulcers with extensive liver damage in infant twins, 471

E

Ectodermal defects with chondrodystrophy, 14
Electro-encephalograph findings in severe enuresis, 316
Ellis, R. W. B., *see* Miller, R. A., and Ellis R. W. B.
Emery, J. L.: Changes in liver in newborn related to physiological icterus (*abstract*), 245
——: Involution of left liver in newborn and its relationship to physiological icterus, 463
——: Muscle fibres in children's stools, 143
——: Pulmonary thrombosis and its association with unexpected death in childhood, 187
——, *see also* Briggs, J. N., Emery, J. L., and Illingworth, R. S.
Empyema thoracis and staphylococcal pneumonia complicated by tension pneumothorax, 42
Encephalopathy following diphtheria-pertussis inoculation, 149
Enuresis, classification of, 392
——, severe, E.E.G. findings in, 316
Eosinophil, circulating, level in full term infants, 140
Epiglottis, primary and secondary abnormalities of, in infants with stridor, 434
Epilepsy, minor, drugs used in treatment of, nephrotoxic effects of (*abstract*), 243
Epiphyses, congenital stippled, 209
Erythema toxicum neonatorum, 404
Erythrogenesis imperfecta, 363
Erythron, peroxidase activity of, in Fanconi's syndrome, 359
Eucalyptus, poisoning by, in childhood, 477

F

Fanconi's syndrome, peroxidase activity of erythron in, 359
Favism in London, 369
Feet and hands, osteomyelitis of all small bones of, 24
Fibro-elastosis, endocardial, left auricular enlargement in, 284
Finlay, H. V. L., and Bound, J. P.: Urticaria neonatorum, 404
Fisher, O. D., and Allen, F. M. B.: Erythrogenesis imperfecta or congenital hypoplastic anaemia (Diamond-Blackfan type), 363
Foetus, rupture of heart of, during labour, 201
Forrester, R. M., *see* Patterson, W. H., and Forrester, R. M.
Frain-Bell, W., *see* Rook, A., and Frain-Bell, W.
Franklin, A. W., and Williamson, D. A. J.: Haemangio-endothelioma with haemorrhage and thrombocytopenia, 490
Fraser, M. S., *see* Craig, J. O., and Fraser, M. S.
——, *see also* MacGillivray, P. C., and Fraser, M. S.
Freer, J. L., and Matheson, W. J.: Left auricular enlargement in endocardial fibro-elastosis, 284

G

Gaisford, W.: B.C.G. vaccination in newborn (*abstract*), 246
Galactosaemia, congenital, liver damage and (*abstract*), 245
Gallagher, E. J., MacGregor, M. E., and Israelski, M.: Chondrodystrophy with ectodermal defects, 14
Galloway, W. H., *see* Smith, J., and Galloway, W. H.
Gardikas, G., Scott, D. G., and Wilkinson, J. F. Observations on foetal haemoglobin, 38
Gastro-enteritis, infantile, strains of *Bact. coli* associated with, sensitivity to antibiotics, 30
——, treatment with antibiotics (*abstract*), 242
Gerrard, J. W., *see* Bower, B. D., Gerrard, J. W., D'Abreu, A. L., and Parsons, C. G.
——, *see also* Davies, B. S., Gerrard, J. W., and Waterhouse, J. A. H.
Gibson, N. K. M., *see* Macrae-Gibson, N. K.
Glucose, blood, patterns in normal infants in first 12 hours of life, 134
Graham, A. L. M., *see* McInroy, R. A., and Graham, A. L. M.
Gray, O. P.: Hydatid disease in childhood (*abstract*), 243
Griffiths, M. I.: Pulmonary atelectasis in young children, 170
Growth, disorders of, in childhood (*abstract*), 244
Gurevitch, J., *see* Shamir, Z., and Gurevitch, J.

H

Hackett, W. R., *see* Bound, J. P., and Hackett, W. R.
Haemangioendothelioma of liver simulating congenital heart disease in infant, 49
—— with haemorrhage and thrombocytopenia, 490
Haematuria, increased, in nephritis during cortisone and A.C.T.H. administration, 213
Haemoglobin, foetal, 38
Haemolytic disease of newborn, 292
—— —— ——, incidence of (*abstract*), 246
—— —— ——, pattern of, 466
Harling, M., *see* Kesson, C. W., and Harling, M.
Hall, E. G., Hay, J. D., Moss, P. D., and Ryan, M. M. P.: Congenital toxoplasmosis in newborn, 117
Hands and feet, osteomyelitis of all small bones of, 24
Haworth, J. C., *see* Keidan, S. E., McCarthy, K., and Haworth, J. C.
Hay, J. D., *see* Hall, E. G., Hay, J. D., Moss, P. D., and Ryan, M. M. P.
Heart, congenital mitral stenosis treated by valvotomy, 91

—— disease, congenital, simulated by haemangio-endothelioma of liver in infant, 49
—— foetal, rupture of, during labour, 201
—— left auricular enlargement in endocardial fibro-elastosis, 284
——, systolic murmurs in infants, incidence and significance of, 52
Hemihypertrophy, congenital, showing variations in bone age and development, 321
Hemiplegia, infantile, sensory defects in (*abstract*), 243
Hernia, umbilical, in infants, 450
HIGASHI, O., KOSEKI, E., and HIGUCHI, M. Case of Fanconi's syndrome with a study of peroxidase activity of the erythron, 26
HIGUCHI, M., *see* HIGASHI, O., KOSEKI, E., and HIGUCHI, M.
HINDEN, E., *see* POULTON, E. M., and HINDEN, E.
Histamine, urinary excretion of, in children, 61
Hodgkin's disease in childhood, 222
HOLZEL, A.: Skin thrush in early infancy, 412
HUBBLE, D. V.: Some disorders of growth in childhood (*abstract*), 244
HUGHES, R., and TODD, R. McL. Intracranial bruits in infants and children, 198
HUISMAN, T. H. J., *see* JONXIS, J. H. P., and HUISMAN, T. H. J.
HUTCHISON, J. H.: Radio-active iodine studies in goitrous cretinism (*abstract*), 243
Hyaluronidase and killed anti-tuberculosis vaccine, 36
Hydatid disease in childhood (*abstract*), 243
Hyperpyrexia in post-kernikterus syndrome, 217
Hypoproteinaemic oedema, idiopathic, and amino-aciduria in infant, 104

I

Icterus, physiological, changes in liver in newborn related to (*abstract*), 245
—— ——, relationship of involution of left liver in newborn to, 463
Ileum, duplication of, 72
ILLINGWORTH, R. S., *see* BRIGGS, J. N., EMERY, J. L., and ILLINGWORTH, R. S.
Infants, feeding of, history of, 151, 232, 332, 416, 495
——, newborn, absorption of chloramphenicol in, 66
—— ——, acute isolated myocarditis in, 288
—— ——, B.C.G. vaccination in (*abstract*), 246
—— ——, blood glucose changes in, 134
—— ——, changes in liver in, related to physiological icterus (*abstract*), 245
—— ——, congenital toxoplasmosis in, 117
—— ——, diphtheria in, 127
—— ——, haemolytic disease of, 292
—— —— —— —— incidence of (*abstract*), 246
—— —— —— —— pattern of, 466
—— ——, involution of left liver in, and its relationship to physiological icterus, 463
—— ——, urticaria of, 404
——, premature, blood sugar studies on, 194
—— ——, growth of, from birth to 4 years, results of national inquiry into, 436
—— ——, human milk and dried cow's milk as foods for (*abstract*), 245
Inoculation, diphtheria-pertussis, encephalography following, 149
Intracranial bruits in infants and children, 198
Intussusception, non-operative reduction of (*abstract*), 246
Iodine, radio-active, studies in goitrous cretinism (*abstract*), 243
ISRAELSKI, M., *see* GALLAGHER, E. J., MACGREGOR, M. E., and ISRAELSKI, M.

J

JACKSON, H., KESSEL, I., JAVETT, S. N., and KUSHLICK, P.: Typhoid osteitis in infancy, 19
JAVETT, S. N., *see* JACKSON, H., KESSEL, I., JAVETT, S. N., and KUSHLICK, P.
JONES, H. E., Recurrent parotitis in children, 182
JONXIS, J. H. P., and BEKIUS, H.: Treatment of ascaris infection with velardon, 329
—— and HUISMAN, T. H. J. Excretion of sugars after intravenous administration of invert sugar, 446

K

KEIDAN, S. E., MCCARTHY, K., and HAWORTH, J. C.: Fatal generalized vaccinia with failure of antibody production and absence of serum gamma globulin, 110
KEMPTON, J. J., and BODIAN, M.: Duodenal ulcers with extensive liver damage in infant twins, 471
KESSEL, I., *see* JACKSON, H., KESSEL, I., JAVETT, S. N., and KUSHLICK, P.
KESSON, C. W., and HARLING, M.: Investigation into certain aspects of pertussis, 409
KIDNEY, haemorrhagic infarction of, treated by nephrectomy, 302
——, thrombosis complicating pink disease cured by nephrectomy, 300
KILLPACK, W. S.: Duplication of ileum, 72
KOSEKI, E., *see* HIGASHI, O., KOSEKI, E., and HIGUCHI, M.
KRAMER, J. G., *see* WHITTEN, W. W., and KRAMER, J. G.
KUSHLICK, P., *see* JACKSON, H., KESSEL, I., JAVETT, S. N., and KUSHLICK, P.

L

Labour, rupture of foetal heart during, 201
Larynx, primary and secondary abnormalities of, in infants with stridor, 434
Laterality crossed, significance and treatment in ordinary school life, 247
LEVICK, C. B., and RUBIE, J.: Haemangioendothelioma of liver simulating congenital heart disease in infant, 49
LEVIN, B., *see* MACKAY, H. M. M., and LEVIN, B.
LIVER, changes in, in newborn related to physiological icterus (*abstract*), 245
——, cirrhosis of, associated with fibrocystic disease of pancreas, 343
—— damage and congenital galactosaemia (*abstract*), 245
—— ——, extensive, in duodenal ulcers in infant twins, 471
——, haemangioendothelioma of, simulating congenital heart disease in infant, 49
——, involution of left, in newborn, and its relationship to physiological icterus, 463
LORBER, J.: Ectopic ossification in tuberculous meningitis, 99
LORD, J. M.: Foetal ascites, 398

M

MACARTHUR, P., *see* MACDONALD, A. M., and MACARTHUR, P.
MCCARTHY, K., *see* KEIDAN, S. E., MCCARTHY, K., and HAWORTH J. C.
MACDONALD, A. M., and MACARTHUR, P.: Foetal vaccinia, 311
MACGILLIVRAY, P. C., and FRASER, M. S.: Boric acid poisoning in infancy arising from treatment of napkin rash, 484
MACGREGOR, M. E., *see* GALLAGHER, E. J., MACGREGOR, M. E., and ISRAELSKI, M.

McINROY, R. A., and GRAHAM, A. L. M.: Rupture of foetal heart during labour, 201
MACKAY, H. M. M., and LEVIN, B.: Human milk and dried cow's milk as foods for premature babies (*abstract*), 245
MACRAE-GIBSON, N. K., and COLES, B. L.: Infantile hypertrophic pyloric stenosis recurring after Rammstedt's operation, 130
Malidone, nephrotoxic effects of (*abstract*), 243
Mandibular dysostosis in African infant, 125
MATHESON, W. J., *see* FREER, J. L., and MATHESON, W. J.
Mediastinum, enterogenous cyst of, 325
Meningitis, tuberculous, ectopic ossification in, 99
Methyl salicylate, poisoning by, in childhood, 480
Metrakos, J. D.: Congenital hypertrophic pyloric stenosis in twins, 351
MICHAELS, L., and WALTERS, G.: Increased haematuria in nephritis during cortisone and A.C.T.H. administration, 213
Milk, human and dried cow's, as foods for premature babies (*abstract*), 245
—— ——, test for adulteration of, 161
MILLER, R. A., and ELLIS, R. W. B.: Tests for adulteration of human milk, 161
MILLICHAP, J. G.: Nephrotoxic effects and other attributes of drugs used in treatment of petit mal (*abstract*), 243
MILLS, W. C. Q., and OWEN, T. K.: Renal thrombosis complicating pink disease, 300
Milontin, nephrotoxic effects of (*abstract*), 243
MITCHELL, R. G., *see* ADAM, H. M., and MITCHELL, R. G.
Mitral stenosis, congenital, treated by valvotomy, 91
MOGFORD, C., *see* DOUGHAS, J. W. B., and MOGFORD, C.
MOSS, P. D., *see* HALL, E. G., HAY, J. D., MOSS, P. D., and RYAN, M. M. P.
Muscle fibres in children's stools, 143
Myocarditis, acute isolated, in newborn infants, 288
——, idiopathic, in infants and children, 271

N

NABARRO, S. N., *see* ROSE, B. S., and NABARRO, S. N.
Napkin rash, boric acid poisoning arising from treatment of, 484
Nephrectomy, haemorrhagic infarction of kidney treated by, 302
——, renal thrombosis complicating pink disease cured by, 300
Nephritis, increased haematuria in, during cortisone and A.C.T.H. administration, 213
Nephrosis, A.C.T.H. in, 372
Newborn infants, absorption of chloramphenicol in, 66
—— ——, acute isolated myocarditis in, 288
—— ——, B.C.G. vaccination in (*abstract*), 246
—— ——, blood glucose patterns in, 134
—— ——, changes in liver in, related to physiological icterus (*abstract*), 245
—— ——, congenital toxoplasmosis in, 117
—— ——, diphtheria in, 127
—— ——, haemolytic disease of, 292
—— —— —— ——, incidence of (*abstract*), 246
—— —— —— ——, pattern of, 466
—— ——, involution of left liver in, and its relationship to physiological icterus, 463
—— ——, urticaria, of, 404

O

O'BRIEN, D.: Absorption of chloramphenicol in the newborn, 66
Oedema, idiopathic hypoproteinaemic, and aminoaciduria in infant, 104
Oils, volatile, poisoning by, in childhood, 475
OLDHAM, J. S.: Two cases of chronic polyneuritis in children, 76
O'REILLY, R. N., *see* WILLIAMS, H., O'REILLY, R. N., WILLIAMS, A.
Ossification, ectopic, in tuberculous meningitis, 99
Osteitis, typhoid, in infancy, 19
Osteomyelitis of all small bones of hands and feet, 24
Ovarian agenesis, 8
OWEN, T. K., *see* MILLS, W. C. Q., and OWEN, T. K.

P

Paedriatric societies in British Isles, 71
Pancreas, fibrocystic disease of, hepatic cirrhosis associated with, 343
PARKINSON, T. J., *see* CREERY R. D. G., and PARKINSON, T. J.
Parotitis, recurrent, in children, 182
PARSONS, C. G., *see* BOWER, B. D., GERRARD, J. W., D'ABREU, A. L., and PARSONS, C. G.
PATTERSON, W. H., and FORRESTER, R. M.: Hyperpyrexia in post-kernikterus syndrome, 217
PEARCE, R. A. H.: Crossed laterality, 247
Peroxidase activity of erythron in Fanconi's syndrome, 359
Pertussis, investigation into certain aspects of, 409
Petit mal, drugs used in treatment of, nephrotoxic effects of (*abstract*), 243
PHILLIPS, H. T.: Some social and ethnic variations in physique of South African nursery school children, 226
PHILPOTT, M. G., and BRIGGS, J. N.: Treatment of Schoenlein-Henoch syndrome with adrenocorticotrophic hormone and cortisone, 57
PICKUP, J. D., *see* CLARK, C. D., and PICKUP, J. D.
Pink disease, renal thrombosis complicating, cured by nephrectomy, 300
Pneumonia, staphylococcal, with empyema thoracis complicated by tension pneumothorax, 42
Pneumonias, atypical, in Ceylonese children, 176
Pneumoperitoneum, diagnostic, 69
Pneumothorax, tension, complicating staphylococcal pneumonia and empyema thoracis, 42
Poisoning, accidental, in childhood, 26, 259
——, boric acid, in infancy, arising from treatment of napkin rash, 484
—— by volatile oils in childhood, 475
Poliomyelitis, acute anterior, response to adrenergic blocking agents and hot pack therapy, 381
Polyneuritis, chronic, in children, 76
Post-kernikterus syndrome, hyperpyrexia in, 217
POULTON, E. M., and HINDEN, E.: Classification of enuresis, 392
Premature babies, blood sugar studies on, 194
—— ——, human milk and dried cow's milk as foods for (*abstract*), 245
—— ——, growth of, from birth to 4 years, results of national inquiry into, 436
—— ——, handicaps of, related to mother's height and weight, 441
Priscoline, response of acute anterior poliomyelitis to, 381
Pterygium syndrome, 8
PUGH, R. J.: Liver damage and congenital galactosaemia (*abstract*), 245
Pulmonary thrombosis and its association with unexpected death in childhood, 187
Pyloric stenosis, congenital hypertrophic, in twins, 351
—— ——, infantile hypertrophic, recurring after Rammstedt's operation, 130
Pyuria in children, 386

R

Rammstedt's operation, infantile hypertrophic pyloric stenosis recurring after, 130
RENDLE-SHORT, J.: Idiopathic renal acidosis in twins, 55
Respirators, mechanical, improvements to (*abstract*), 244
Retroperitoneal teratoma in infancy, 147
ROOK, A., and FRAIN-BELL, W.: Papular urticaria, 304
ROSE, B. S., and NABARRO, S. N.: Four cases of acute acquired haemolytic anaemia in childhood treated with A.C.T.H., 87
RUBIE, J.: Diagnostic pneumoperitoneum, 69
——, *see also* LEVICK, C. B., and RUBIE, J.
RYAN, M. M. P., *see* HALL, E. G., HAY, J. D., MOSS, P. D., and RYAN, M. M. P.

S

SAINSBURY, H.: The estimation of blood pressure in childhood with special reference to the choice of standard cuffs, 268
SALE, T. A.: Enterogenous cyst of mediastinum, 325
SALVIOLI, G.: Killed anti-tuberculosis vaccine and hyaluronidase (diffusing vaccine), 36
Sassafras, poisoning by, in childhood, 478
Schoenlein-Henoch syndrome, treatment with adrenocorticotrophic hormone and cortisone, 57
SCOTT, D. G., *see* GARDIKAS, G., SCOTT, D. G., and WILKINSON, J. F.
Scurvy, early, radiographic manifestations of, 81
Serum gamma globulin, absence of, and failure of antibody production in fatal generalized vaccinia, 110
SHAMIR, Z., and GUREVITCH, J.: Thirty-eight cases of haemolytic disease of the newborn, 292
SHORT, J. R., *see* RENDLE-SHORT, J.
Skin thrush in early infancy, 412
SKJELBRED, P.: Ovarian agenesis or the pterygium syndrome, 8
SMITH, J., and GALLOWAY, W. H.: Sensitivity to antibiotics of strains of *Bact. coli* associated with infantile gastro-enteritis, 30
SMITH, R. E.: Improvements to mechanical respirators (*abstract*), 244
SMITHELLS, R. W.: Vascular ring: cause of congenital stridor, 204
Societies, paediatric, in British Isles, 71
South African nursery school children, social and ethnic variations in physique of, 226
SPEAR, A. B., *see* TURTON, E. C., and SPEAR, A. B.
SPENCER, R.: Case of tension pneumothorax complicating staphylococcal pneumonia and empyema thoracis, 42
Spolverini, Professor Luigi, 80th birthday of, 240
STANSFIELD, J. M., and WEBB, J. K. G.: Observations on pyuria in children, 386
Stools, children's, muscle fibres in, 143
Stridor, congenital, vascular ring as cause of, 204
——, infantile, 423
—— ——, aetiological classification of, 434
—— ——; follow-up survey (*abstract*), 244
Sugars, excretion of, after intravenous administration of invert sugar, 446
SUTHERLAND, J. M.: Encephalopathy following diphtheria-pertussis inoculation, 149
SWINSCOW, D.: Accidental poisoning of young children, 26

T

TAYLOR, W. C.: Incidence and significance of systolic cardiac murmurs in infants, 52
Teratoma, retroperitoneal, in infancy, 147
Terramycin, effect on faecal flora of children in institution, 33
Thrombocytopenia and haemorrhage with haemangio-endothelioma, 490
Thrombosis, pulmonary, and its association with unexpected death in children, 187
——, renal, complicating pink disease, cured by nephrectomy, 300
Thrush, skin, in early infancy, 412
TIZARD, J. P. M.: Sensory defects in infantile hemiplegia (*abstract*), 243
TODD, R. MCL., *see* HUGHES, R., and TODD, R. MCL.
Toxoplasmosis, congenital, in newborn, 117
Tridione, nephrotoxic effects of (*abstract*), 243
Turpentine, poisoning by, in childhood, 479
TURTON, E. C., and SPEAR, A. B.: E.E.G. findings in 100 cases of severe enuresis, 316
Twins, congenital hypertrophic pyloric stenosis in, 351
——, infant, duodenal ulcers with extensive liver damage in, 471
Typhoid osteitis in infancy, 19

U

Urticaria neonatorum, 404
——, papular, 304

V

Vaccine, killed anti-tuberculosis, and hyaluronidase, 36
Vaccinia, foetal, 311
—— generalized, fatal, with failure of antibody production and absence of serum gamma globulin, 110
Vascular ring; a cause of congenital stridor, 204
Velardon, treatment of ascaris infection with, 329
Vitello-intestinal duct, remnants of, 1

W

WALKER, W.: Studies in incidence, with results, in haemolytic disease of newly born (*abstract*), 246
WALTERS, G., *see* MICHAELS, L., and WALTERS, G.
WARD, O. C.: Blood sugar studies on premature babies, 194
WATERHOUSE, J. A. H., *see* DAVIES, B. S., GERRARD, J. W., and WATERHOUSE, J. A. H.
WAYBURNE, S.: Mandibular dysostosis in African infant, 125
WEBB, J. K. G., *see* STANSFIELD, J. M., and WEBB, J. K. G.
WEBSTER, R., and WILLIAMS, H.: Hepatic cirrhosis associated with fibrocystic disease of pancreas, 343
WHITTEN, W. W., and KRAMER, J. G.: The response of acute anterior poliomyelitis to adrenergic blocking agents and hot pack therapy, 381
WICKES, I. G.: History of infant feeding, 151, 232, 332, 416, 495
WILKINSON, J. F., *see* GARDIKAS, G., SCOTT, D. G., and WILKINSON, J. F.
WILLIAMS, A., *see* WILLIAMS, H., O'REILLY, R. N., and WILLIAMS, A.
WILLIAMS, H., O'REILLY, R. N., and WILLIAMS, A.: Fourteen cases of idiopathic myocarditis in infants and children, 271
——, *see also* WEBSTER, R., and WILLIAMS, H.
WILLIAMSON, D. A. J., *see* FRANKLIN, A. W., and WILLIAMSON, D. A. J.
WILSON, H. E. C., *see* ARNEIL, G. C., and WILSON, H. E. C.

Wintergreen, oil of, poisoning by, in childhood, 480
Woods, G. E.: Some observations on umbilical hernia in infants, 450
Wylie, M. E. S.: Case of congenital diabetes, 297

Z

Zachary, R. B.: Non-operative reduction of intussusception (*abstract*), 246

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